Health & Drugs

Disease, Prescription & Medication

Nicolae Sfetcu

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A *drug* is any biological substance, synthetic or non-synthetic, that is taken for non-dietary needs. It is usually synthesized outside of an organism, but introduced into an organism to produce its action. That is, when taken into the organisms body, it will produce some effects or alter some bodily functions (such as relieving symptoms, curing diseases or used as preventive medicine or any other purposes).

Note that natural endogenous biochemicals (such as hormones) can bind to the same receptor in the cell, producing the same effect as a drug. Thus, drug is merely an artificial definition that distinguishes whether that molecule is synthesized within an organism or outside an organism. For instance, insulin is a hormone that is synthesized in the body; it is considered as a hormone when it is synthesized by the pancreas inside the body, but if it is introduced into the body from outside, it is considered as a drug.

It is a substance which is not food, and which, when ingested, affects the functioning of the mind, or the body, or both. However, under the philosophy of Chinese medicine, food is also considered a drug as it affects particular parts of body and cures some diseases. Thus, food does satisfy the above definition of drug so long as ingestion of it would alter some bodily functions.

Contents

Health

Health is the functional and/or metabolic efficiency of an organism, at any moment in time, at both the cellular and global levels. All individual organisms, from the simplest to the most complex, vary between optimum health and zero health (dead).

In the medical field, health is commonly defined as an organism's ability to efficiently respond to challenges (stressors) and effectively restore and sustain a "state of balance," known as homeostasis.

Another widely accepted definition of health is that of the World Health Organization "WHO". It states that "health is a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity"[1]. In more recent years, this statement has been modified to include the ability to lead a "socially and economically productive life." The WHO definition is not without criticism, as some argue that health cannot be defined as a state at all, but must be seen as a process of continuous adjustment to the changing demands of living and of the changing meanings we give to life. The WHO definition is therefore considered by many as an idealistic goal rather than a realistic proposition.

The LaLonde report suggested that there are four general determinants of health which he called "human biology", "environment", "lifestyle", and "healthcare organization"[2] Thus, health is maintained through the science and practice of medicine, but can also be improved by individual effort. Physical fitness, weight loss, healthy eating, stress management training and stopping smoking and other substance abuse are examples of steps to improve one's health. Workplace programs are recognized by an increasingly large number of companies for their value in improving health and well-being of their employees, and increasing morale, loyalty and productivity at work. A company may provide a gym with exercise equipment, start smoking cessation programs, provide nutrition, weight or stress management training. Other programs may include health risk assessments, health screenings and body mass index monitoring.

An increasing measure of the health of populations is height, which is strongly regulated by nutrition and health care, among other standard of living and quality of life matters. The study of human growth, its regulators and its implications is known as auxology.

Wellness is a term sometimes used to describe the psychological state of being healthy, but is most often used in the field of alternative medicine to describe one's state of being.

Exercise

Physical exercise is the performance of some activity in order to develop or maintain physical fitness and overall health. It is often directed toward also honing athletic ability or skill. Frequent and regular physical exercise is an important component in the prevention of some of the diseases of affluence such as cancer, heart disease, cardiovascular disease, Type 2 diabetes and obesity.

Exercises are generally grouped into three types depending on the overall effect they have on the human body:

- Flexibility exercises such as stretching improve the range of motion of muscles and joints.
- Aerobic exercises such as walking and running focus on increasing cardiovascular endurance.
- Anaerobic exercises such as weight training or sprinting increase short-term muscle strength.

Physical exercise is considered important for maintaining physical fitness including healthy weight; building and maintaining healthy bones, muscles, and joints; promoting physiological well-being; reducing surgical risks; and strengthening the immune system.

Proper nutrition is at least as important to health as exercise. When exercising it becomes even more important to have good diet to ensure the body has the correct ratio of macronutrients whilst providing ample micronutrients, this is to aid the body with the recovery process following strenuous exercise. When the body falls short of proper nutrition, it gets into starvation mode developed through evolution and depends onto fat content for survival. Research suggest that the production of thyroid hormones can be negatively affected by repeated bouts of dieting and calorie restriction[3].

Proper rest and recovery is also as important to health as exercise, otherwise the body exists in a permanently injured state and will not improve or adapt adequately to the exercise.

The above two factors can be compromised by psychological compulsions (eating disorders such as exercise bulimia, anorexia, and other bulimias), misinformation, a lack of organization, or a lack of motivation. These all lead to a decreased state of health.

Delayed Onset Muscle Soreness can occur after any kind of exercise, particularly if the body is in an unconditioned state relative to that exercise.

Hygiene

Hygiene is the maintenance of healthy practices. In modern terminology, this is usually regarded as a particular reference to cleanliness. The term Hygiene originates as a reference to Hygieia, who was a daughter of Asclepius and the goddess of health, cleanliness and sanitation. The related term *personal grooming/grooming* means to enhance one's physical appearance or appeal for others, by removing obvious imperfections in one's appearance or improving one's hygiene.

Outward signs of good hygiene include the absence of visible dirt (including dust and stains on clothing) or of bad odor/smells. Since the development of the germ theory of disease, hygiene has come to mean any practice leading to the absence of harmful levels of bacteria.

Good hygiene is an aid to health, beauty, comfort, and social interactions. It directly aids in disease prevention and/or disease isolation. (That is, good hygiene will help keep one healthy and thus avoid illness. If one is ill, good hygiene can reduce one's contagiousness to others.)

Washing (with water) is the most common example of hygienic behavior. Washing is often done with soap or detergent which helps to remove oils and to break up dirt particles so they may be washed away.

Hygienic practices—such as frequent hand washing or the use of boiled (and thus sterilized) water in surgery/medical operations—have a profound impact on reducing the spread of disease. This is because they kill or remove disease-causing microbes (germs) in the immediate surroundings. For instance, washing one's hands after using the toilet and before handling food reduces the chance of spreading E. coli bacteria and Hepatitis A, both of which are spread from fecal contamination of food.

Adequate hygiene requires an adequate and convenient supply of clean water. In much of the developing world maintaining an acceptable level of cleanliness is difficult or impossible for much of the population due to lack of adequate water supply and sanitation. This results in the rapid spread and extent of diseases such as trachoma which are rare in the developed world.

Nutrition

Nutrition is a science which studies the relationship between diet and states of health and disease. Dieticians are Health professionals who are specialized in this area of expertise. They are also the only highly trained health professionals able to provide safe, evidence-based and accurate dietary advice and interventions.

Between the extremes of optimal health and death from starvation or malnutrition, there is an array of disease states that can be caused or alleviated by changes in diet. Deficiencies, excesses and imbalances in diet can produce negative impacts on health, which may lead to diseases such as scurvy, obesity or osteoporosis, as well as psychological and behavioral problems. Moreover, excessive ingestion of elements that have no apparent role in health, (e.g. lead, mercury, PCBs, dioxins), may incur toxic and potentially lethal effects, depending on the dose. The science of nutrition attempts to understand how and why specific dietary aspects influence health.

Mental health

Mental health is a concept refers to a human individual's emotional and psychological well-being. Merriam-Webster defines mental health as "A state of emotional and psychological well-being in which an individual is able to use his or her cognitive and emotional capabilities, function in society, and meet the ordinary demands of everyday life."

According to the World Health Organization (WHO), there is no one "official" definition of mental health. Cultural differences, subjective assessments, and competing professional theories all affect how "mental health" is defined. In general, most experts agree that "mental health" and "mental illness" are not opposites. In other words, the absence of a recognized mental disorder is not necessarily an indicator of mental health.

One way to think about mental health is by looking at how effectively and successfully a person functions. Feeling capable and competent; being able to handle normal levels of stress, maintain satisfying relationships, and lead an independent life; and being able to "bounce back," or recover from difficult situations, are all signs of mental health.

See also

- Dietary supplements
    - Nootropics
    - Vitamins

References

1. ^ WHO. Constitution of the World Health Organization , Geneva, 1946. Accessed October 30, 2006.
2. ^ Lalonde, Marc. "A New Perspective on the Health of Canadians." Ottawa: Minister of Supply and Services; 1974.
3. ^ Common fitness mistakes people make Stay Fit retrived on 11-13-2006

- WHO (1979) Health for All, Sr. Nos. 1, 2

Health science

Health science is the discipline of applied science which deals with human and animal health. There are two parts to health science: the study, research, and knowledge of health and the application of that knowledge to improve health, cure diseases, and understanding how humans and animals function. Research builds primarily on the pure sciences of biology, chemistry, and physics as well as social sciences (for example medical sociology). Other fields which made an exceptionally significant contribution to the health sciences include biochemistry, biotechnology, engineering, epidemiology, genetics, nursing, pharmacology, pharmacy, public health, and medicine. The health sciences industry, a multi-billion dollar business, is a subset of the life sciences, medical care, and diagnosis industries.

Historical overview

The foundations for the health science fields are as old as the human race. Humans have always been in need of solutions to address illness, injury, and various health related issues such as childbirth. With modern technology and the backing of the pure sciences, the scientific accuracy of these fields has greatly improved. Nevertheless, many cultures have used and continue to use various herbs and other culturally specific solutions to help solve health problems that may or may not be backed by any scientific support.

Application of health-related knowledge

Health deliveries

There are a large number of health professions. The terms medicine or biomedicine, and medical doctor or M.D. refer to dominant conventional practices in the West.

There are a wide range of traditional areas of health science. The most common areas are: medicine, nursing, midwifery, and various forms of therapy to supplement the healing process and restore proper activity (e.g. Dietetics, recreational, physical, occupational, speech, and respiratory). Health science includes both the study and application of preventing and curing human diseases and disorders. Medical doctors include physicians and surgeons. There are many different branches of medicine; the other health care professions also have specialties or focus on specific populations or settings of care. Public health studies the effect of environmental factors such as available health care resources on the health of the general population, often focusing on particular populations, such as mothers and children. Dietitians educate people about proper nutrition, particularly specific dietary needs of populations such as people with diabetes, breastfeeding women, and people with celiac disease. Other less common medical areas include first aid and triage.

Dental health has grown in importance in recent decades making dentistry a major field of health sciences. Counselling, hospice care, home care, nutrition, medical social work, alternative medicine, pharmacology, and toxicology are all considered part of health science.

Veterinary medicine is the health science dedicated exclusively to the care of animals. Veterinary medicine is involved in preventing and curing animal diseases and disorders, inspecting animal originated food (like milk and meat) and animal husbandry.

Contemporary themes

Because health science deals with human life, issues of medical ethics, an important area of ethics, arise frequently. Medical ethics includes questions on topics such as a patient's right to privacy. Euthanasia, abortion, human cloning, stem cell research and genetic engineering are especially controversial issues directly related to health science.

See also

- Pharmaceutical industry

External links and references

- National Institute of Environmental Health Sciences
- The US National Library of Medicine
- Biomedical News on Stem Cell Research

Medicine

Medicine is the branch of health science and the sector of public life concerned with maintaining or restoring human health through the study, diagnosis, treatment and possible prevention of disease and injury. It is both an area of knowledge – a science of body systems, their diseases and treatment – and the applied practice of that knowledge.

Overview

Western medical care is shared between medical professionals (physicians) and other professionals such as physician assistants, nurses and pharmacists, sometimes known as allied health professionals. Historically, only those with a medical doctorate have been considered to practice medicine. Clinicians (licensed professionals who deal with patients) can be physicians, nurses, therapists or others. The medical profession is the social and occupational structure of the group of people formally trained and authorized to apply medical knowledge. Many countries and legal jurisdictions have legal limitations on who may practice medicine.

Medicine comprises various specialized sub-branches, such as cardiology, pulmonology, neurology, or other fields such as sports medicine, research or public health.

Human societies have had various different systems of health care practice since at least the beginning of recorded history. Medicine, in the modern period, is the mainstream scientific tradition which developed in the Western world since the early Renaissance (around 1450). Many other traditions of health care are still practiced throughout the world; most of these are separate from Western medicine, which is also called *biomedicine*, *allopathic medicine* or the Hippocratic tradition. The most highly developed of these are traditional Chinese medicine, Tibetan medicine and the Ayurvedic traditions of India and Sri Lanka. Various non-mainstream traditions of health care have also developed in the Western world. These systems are sometimes considered companions to Hippocratic medicine, and sometimes are seen as competition to the Western tradition. Few of them have any scientific confirmation of their tenets, because if they did they would be brought into the fold of Western medicine.

"Medicine" is also often used amongst medical professionals as shorthand for internal medicine. Veterinary medicine is the practice of health care in animal species other than human beings.

History of medicine

The earliest type of medicine in most cultures was the use of plants (Herbalism) and animal parts. This was usually in concert with 'magic' of various kinds in which: animism (the notion of inanimate objects having spirits); spiritualism (here meaning an appeal to gods or communion with ancestor spirits); shamanism (the vesting of an individual with mystic powers); and divination (the supposed obtaining of truth by magic means), played a major role.

The practice of medicine developed gradually, and separately, in ancient Egypt, India, China, Greece, Persia and elsewhere. Medicine as it is practiced now developed largely in the late eighteenth century and early nineteenth century in England (William Harvey, seventeenth century), Germany (Rudolf Virchow) and France (Jean-Martin Charcot, Claude Bernard and others). The new, "scientific" medicine (where results are testable and repeatable) replaced early Western traditions of medicine, based on herbalism, the Greek "four humours" and other pre-modern theories.[citation needed] The focal points of development of clinical medicine shifted to the United Kingdom and the USA by the early

1900s (Canadian-born)Sir William Osler, Harvey Cushing). Possibly the major shift in medical thinking was the gradual rejection in the 1400's of what may be called the 'traditional authority' approach to science and medicine. This was the notion that because some prominent person in the past said something must be so, then that was the way it was, and anything one observed to the contrary was an anomaly (which was paralleled by a similar shift in European society in general - see Copernicus's rejection of Ptolemy's theories on astronomy). People like Vesalius led the way in improving upon or indeed rejecting the theories of great authorities from the past such as Galen, Hippocrates, and Avicenna/Ibn Sina, all of whose theories were in time almost totally discredited. Such new attitudes were also only made possible by the weakening of the Roman Catholic church's power in society, especially in the Republic of Venice.

Evidence-based medicine is a recent movement to establish the most effective algorithms of practice (ways of doing things) through the use of the scientific method and modern global information science by collating all the evidence and developing standard protocols which are then disseminated to healthcare providers. One problem with this 'best practice' approach is that it could be seen to stifle novel approaches to treatment.

Genomics and knowledge of human genetics is already having some influence on medicine, as the causative genes of most monogenic genetic disorders have now been identified, and the development of techniques in molecular biology and genetics are influencing medical practice and decision-making.

Pharmacology has developed from herbalism and many drugs are still derived from plants (atropine, ephedrine, warfarin, aspirin, digoxin, vinca alkaloids, taxol, hyoscine, etc). The modern era really began with Koch's discoveries around 1880 of the transmission of disease by bacteria, and then the discovery of antibiotics shortly thereafter around 1900. The first major class of antibiotics was the sulfa drugs, derived originally from azo dyes. Throughout the twentieth century, major advances in the treatment of infectious diseases were observable in (Western) societies. The medical establishment is now developing drugs that are targeted towards one particular disease process. Thus drugs are being developed to minimise the side effects of prescribed drugs, to treat cancer, geriatric problems, long-term problems (such as high cholesterol), chronic diseases (type 2 diabetes), lifestyle and degenerative diseases such as (arthritis) and Alzheimer's disease.

Practice of medicine

The practice of medicine combines both science as the evidence base and art in the application of this medical knowledge in combination with intuition and clinical judgement to determine the treatment plan for each patient.

Central to medicine is the patient-physician relationship established when a person with a health concern seeks a physician's help; the 'medical encounter'. Other health professionals similarly establish a relationship with a patient and may perform various interventions, e.g. nurses, radiographers and therapists.

As part of the medical encounter, the healthcare provider needs to:

- develop a relationship with the patient

- gather data (medical history, systems enquiry, and physical examination, combined with laboratory or imaging studies (investigations))
- analyze and synthesize that data (assessment and/or differential diagnoses), and then:
- develop a treatment plan (further testing, therapy, watchful observation, referral and follow-up)
- treat the patient accordingly
- assess the progress of treatment and alter the plan as necessary (management).

The medical encounter is documented in a medical record, which is a legal document in many jurisdictions.[1]

Health care delivery systems

Medicine is practiced within the medical system, which is a legal, credentialing and financing framework, established by a particular culture or government. The characteristics of a health care system have significant effect on the way medical care is delivered.

Financing has a great influence as it defines who pays the costs. Aside from tribal cultures, the most significant divide in developed countries is between universal health care and market-based health care (such as practiced in the U.S.). Universal health care might allow or ban a parallel private market. The latter is described as single-payor system.

Transparency of information is another factor defining a delivery system. Access to information on conditions, treatments, quality and pricing greatly affects the choice by patients / consumers and therefore the incentives of medical professionals. While US health care system has come under fire for lack of openness, new legislation may encourage greater openness. There is a perceived tension between the need for transparency on the one hand and such issues as patient confidentiality and the possible exploitation of information for commercial gain on the other.

Health care delivery

Medical care delivery is classified into primary, secondary and tertiary care.

Primary care medical services are provided by physicians or other health professionals who has first contact with a patient seeking medical treatment or care. These occur in physician's office, clinics, nursing homes, schools, home visits and other places close to patients. About 90% of medical visits can be treated by the primary care provider. These include treatment of acute and chronic illnesses, preventive care and health education for all ages and both sexes.

Secondary care medical services are provided by medical specialists in their offices or clinics or at local community hospitals for a patient referred by a primary care provider who first diagnosed or treated the patient. Referrals are made for those patients who required the expertise or procedures performed by specialists. These include both ambulatory care and inpatient services, emergency rooms, intensive care medicine, surgery services, physical therapy, labor and delivery, endoscopy units, diagnostic laboratory and medical imaging

services, hospice centers, etc. Some primary care providers may also take care of hospitalized patients and deliver babies in a secondary care setting.

Tertiary care medical services are provided by specialist hospitals or regional centers equipped with diagnostic and treatment facilities not generally available at local hospitals. These include trauma centers, burn treatment centers, advanced neonatology unit services, organ transplants, high-risk pregnancy, radiation oncology, etc.

Modern medical care also depends on information - still delivered in many health care settings on paper records, but increasingly nowadays by electronic means.

Physician-patient relationship

The physician-patient relationship and interaction is a central process in the practice of medicine. There are many perspectives from which to understand and describe it.

An idealized physician's perspective, such as is taught in medical school, sees the core aspects of the process as the physician learning the patient's symptoms, concerns and values; in response the physician examines the patient, interprets the symptoms, and formulates a diagnosis to explain the symptoms and their cause to the patient and to propose a treatment. The job of a physician is similar to a human biologist: that is, to know the human frame and situation in terms of normality. Once the physician knows what is normal and can measure the patient against those norms, he or she can then determine the particular departure from the normal and the degree of departure. This is called the diagnosis.

The four great cornerstones of diagnostic medicine are anatomy (structure: what is there), physiology (how the structure/s work), pathology (what goes wrong with the anatomy and physiology) and psychology (mind and behaviour). In addition, the physician should consider the patient in their 'well' context rather than simply as a walking medical condition. This means the socio-political context of the patient (family, work, stress, beliefs) should be assessed as it often offers vital clues to the patient's condition and further management. In more detail, the patient presents a set of complaints (the symptoms) to the physician, who then obtains further information about the patient's symptoms, previous state of health, living conditions, and so forth. The physician then makes a review of systems (ROS) or systems enquiry, which is a set of ordered questions about each major body system in order: general (such as weight loss), endocrine, cardio-respiratory, etc. Next comes the actual physical examination; the findings are recorded, leading to a list of possible diagnoses. These will be in order of probability. The next task is to enlist the patient's agreement to a management plan, which will include treatment as well as plans for follow-up. Importantly, during this process the healthcare provider educates the patient about the causes, progression, outcomes, and possible treatments of his ailments, as well as often providing advice for maintaining health. This teaching relationship is the basis of calling the physician doctor, which originally meant "teacher" in Latin. The patient-physician relationship is additionally complicated by the patient's suffering (patient derives from the Latin patior, "suffer") and limited ability to relieve it on his/her own. The physician's expertise comes from his knowledge of what is healthy and normal contrasted with knowledge and experience of other people who have suffered similar symptoms (unhealthy and abnormal), and the proven ability to relieve it with medicines (pharmacology) or other therapies about

which the patient may initially have little knowledge, although the latter may be better performed by a pharmacist.

The physician-patient relationship can be analyzed from the perspective of ethical concerns, in terms of how well the goals of non-maleficence, beneficence, autonomy, and justice are achieved. Many other values and ethical issues can be added to these. In different societies, periods, and cultures, different values may be assigned different priorities. For example, in the last 30 years medical care in the Western World has increasingly emphasized patient autonomy in decision making.

The relationship and process can also be analyzed in terms of social power relationships (e.g., by Michel Foucault), or economic transactions. Physicians have been accorded gradually higher status and respect over the last century, and they have been entrusted with control of access to prescription medicines as a public health measure. This represents a concentration of power and carries both advantages and disadvantages to particular kinds of patients with particular kinds of conditions. A further twist has occurred in the last 25 years as costs of medical care have risen, and a third party (an insurance company or government agency) now often insists upon a share of decision-making power for a variety of reasons, reducing freedom of choice of healthcare providers and patients in many ways.

The quality of the patient-physician relationship is important to both parties. The better the relationship in terms of mutual respect, knowledge, trust, shared values and perspectives about disease and life, and time available, the better will be the amount and quality of information about the patient's disease transferred in both directions, enhancing accuracy of diagnosis and increasing the patient's knowledge about the disease. Where such a relationship is poor the physician's ability to make a full assessment is compromised and the patient is more likely to distrust the diagnosis and proposed treatment. In these circumstances and also in cases where there is genuine divergence of medical opinions, a second opinion from another physician may be sought.

In some settings, e.g. the hospital ward, the patient-physician relationship is much more complex, and many other people are involved when somebody is ill: relatives, neighbors, rescue specialists, nurses, technical personnel, social workers and others.

Clinical skills

A complete medical evaluation includes a medical history, a systems enquiry, a physical examination, appropriate laboratory or imaging studies, analysis of data and medical decision making to obtain diagnoses, and a treatment plan.[2]

The components of the medical history are:

- Chief complaint (CC): the reason for the current medical visit. These are the 'symptoms.' They are in the patient's own words and are recorded along with the duration of each one. Also called 'presenting complaint.'
- History of present illness / complaint (HPI): the chronological order of events of symptoms and further clarification of each symptom.
- Current activity: occupation, hobbies, what the patient actually does.

- Medications: what drugs the patient takes including over-the-counter, and home remedies, as well as herbal medicines/herbal remedies such as St. John's Wort. Allergies are recorded.
- Past medical history (PMH/PMHx): concurrent medical problems, past hospitalizations and operations, injuries, past infectious diseases and/or vaccinations, history of known allergies.
- Social history (SH): birthplace, residences, marital history, social and economic status, habits (including diet, medications, tobacco, alcohol).
- Family history (FH): listing of diseases in the family that may impact the patient. A family tree is sometimes used.
- Review of systems (ROS) or systems enquiry: an set of additional questions to ask which may be missed on HPI, generally following the body's main organ systems (heart, lungs, digestive tract, urinary tract, etc).

The physical examination is the examination of the patient looking for signs of disease ('Symptoms' are what the patient volunteers, 'signs' are what the healthcare provider detects by examination). The healthcare provider uses the senses of sight, hearing, touch, and sometimes smell (taste has been made redundant by the availability of modern lab tests). Four chief methods are used: inspection, palpation (feel), percussion (tap to determine resonance characteristics), and auscultation (listen); smelling may be useful (e.g. infection, uremia, diabetic ketoacidosis). The clinical examination involves study of:

- Vital signs including height, weight, body temperature, blood pressure, pulse, respiration rate, hemoglobin oxygen saturation
- General appearance of the patient and specific indicators of disease (nutritional status, presence of jaundice, pallor or clubbing)
- Skin
- Head, eye, ear, nose, and throat (HEENT)
- Cardiovascular (heart and blood vessels)
- Respiratory (large airways and lungs)
- Abdomen and rectum
- Genitalia (and pregnancy if the patient is or could be pregnant)
- Musculoskeletal (spine and extremities)
- Neurological (consciousness, awareness, brain, cranial nerves, spinal cord and peripheral nerves)
- Psychiatric (orientation, mental state, evidence of abnormal perception or thought)

Laboratory and imaging studies results may be obtained, if necessary.

The medical decision-making (MDM) process involves analysis and synthesis of all the above data to come up with a list of possible diagnoses (the differential diagnoses), along with an idea of what needs to be done to obtain a definitive diagnosis that would explain the patient's problem.

The treatment plan may include ordering additional laboratory tests and studies, starting therapy, referral to a specialist, or watchful observation. Follow-up may be advised.

This process is used by primary care providers as well as specialists. It may take only a few minutes if the problem is simple and straightforward. On the other hand, it may take

weeks in a patient who has been hospitalized with bizarre symptoms or multi-system problems, with involvement by several specialists.

On subsequent visits, the process may be repeated in an abbreviated manner to obtain any new history, symptoms, physical findings, and lab or imaging results or specialist consultations.

Branches of medicine

Working together as an interdisciplinary team, many highly trained health professionals besides medical practitioners are involved in the delivery of modern health care. Some examples include: nurses, laboratory scientists, pharmacists, physiotherapists, respiratory therapists, speech therapists, occupational therapists, dietitians and bioengineers.

The scope and sciences underpinning human medicine overlap many other fields. Dentistry and psychology, while separate disciplines from medicine, are considered medical fields.

Midlevel Practitioner

Physician assistants, nurse practitioners and midwives treat patients and prescribe medication in many legal jurisdictions.

Veterinary Medicine

Veterinarians applies similar techniques as physicians to the care of animals.

Physicians have many specializations and subspecializations which are listed below. There are variations from country to country regarding which specialities certain subspecialities are in.

Diagnostic specialties

- Clinical laboratory sciences are the clinical diagnostic services which apply laboratory techniques to diagnosis and management of patients. In the United States these services are supervised by a pathologist. The personnel that work in these medical laboratory departments are technically trained staff, each of whom usually hold a medical technology degree, who actually perform the tests, assays, and procedures needed for providing the specific services.
- Pathology is the branch of medicine that deals with the study of diseases and the morphologic, physiologic changes produced by them. As a diagnostic specialty, pathology can be considered the basis of modern scientific medical knowledge and plays a large rôle in evidence-based medicine. Many modern molecular tests such as flow cytometry, polymerase chain reaction (PCR), immunohistochemistry, cytogenetics, gene rearragements studies and fluorescent in situ hybridization (FISH) fall within the territory of pathology.

- Radiology is concerned with imaging of the human body, e.g. by x-rays, x-ray computed tomography, ultrasonography, and nuclear magnetic resonance tomography.

Clinical disciplines

- Anesthesiology (AE) or anaesthesia (BE) is the clinical discipline concerned with providing anesthesia. Pain medicine is often practiced by specialised anesthesiologists.
- Dermatology is concerned with the skin and its diseases. In the UK, dermatology is a subspeciality of general medicine.
- Emergency medicine is concerned with the diagnosis and treatment of acute or life-threatening conditions, including trauma, surgical, medical, pediatric, and psychiatric emergencies.
- General practice, family practice, family medicine or primary care is, in many countries, the first port-of-call for patients with non-emergency medical problems. Family practitioners are usually able to treat over 90% of all complaints without referring to specialists.
- Hospital medicine is the general medical care of hospitalized patients. Physicians whose primary professional focus is hospital medicine are called hospitalists in the USA.
- Internal medicine is concerned with systemic diseases of adults, i.e. those diseases that affect the body as a whole (restrictive, current meaning), or with all adult non-operative somatic medicine (traditional, inclusive meaning), thus excluding pediatrics, surgery, gynecology and obstetrics, and psychiatry. There are several subdisciplines of internal medicine:
    - Cardiology
    - Endocrinology
    - Gastroenterology
    - Hematology
    - Infectious Diseases
    - Intensive care medicine
    - Nephrology
    - Oncology
    - Pulmonology
    - Rheumatology
- Neurology is concerned with the diagnosis and treatment of nervous system diseases. It is a subspeciality of general medicine in the UK.
- Obstetrics and gynecology (often abbreviated as Ob/Gyn) are concerned respectively with childbirth and the female reproductive and associated organs. Reproductive medicine and fertility medicine are generally practiced by gynecological specialists.

- Palliative care is a relatively modern branch of clinical medicine that deals with pain and symptom relief and emotional support in patients with terminal illnesses including cancer and heart failure.
- Pediatrics (AE) or paediatrics (BE) is devoted to the care of infants, children, and adolescents. Like internal medicine, there are many pediatric subspecialities for specific age ranges, organ systems, disease classes, and sites of care delivery. Most subspecialities of adult medicine have a pediatric equivalent such as pediatric cardiology, pediatric endocrinology, pediatric gastroenterology, pediatric hematology, pediatric oncology, pediatric ophthalmology, and neonatology.
- Physical medicine and rehabilitation (or physiatry) is concerned with functional improvement after injury, illness, or congenital disorders.
- Preventive medicine is the branch of medicine concerned with preventing disease.
- Psychiatry is the branch of medicine concerned with the bio-psycho-social study of the etiology, diagnosis, treatment and prevention of cognitive, perceptual, emotional and behavioral disorders. Related non-medical fields include psychotherapy and clinical psychology.
- Radiation therapy is concerned with the therapeutic use of ionizing radiation and high energy elementary particle beams in patient treatment.
- Radiology is concerned with the interpretation of imaging modalities including x-rays, ultrasound, radioisotopes, and MRI (Magnetic Resonance Imaging). A newer branch of radiology, interventional radiology, is concerned with using medical devices to access areas of the body with minimally invasive techniques.
- Surgical specialties employ operative treatment. These include Orthopedics, Urology, Ophthalmology, Neurosurgery, Plastic Surgery, Otolaryngology and various subspecialties such as transplant and cardiothoracic. Some disciplines are highly specialized and are often not considered subdisciplines of surgery, although their naming might suggest so.
- Urgent care focuses on delivery of unscheduled, walk-in care outside of the hospital emergency department for injuries and illnesses that are not severe enough to require care in an emergency department.
- Gender-based medicine studies the biological and physiological differences between the human sexes and how that affects differences in disease.

Interdisciplinary fields

Interdisciplinary sub-specialties of medicine are:

- Aerospace medicine deals with medical problems related to flying and space travel.
- Bioethics is a field of study which concerns the relationship between biology, science, medicine and ethics, philosophy and theology.

- Biomedical Engineering is a field dealing with the application of engineering principles to medical practice.
- Clinical pharmacology is concerned with how systems of therapeutics interact with patients.
- Conservation medicine studies the relationship between human and animal health, and environmental conditions. Also known as ecological medicine, environmental medicine, or medical geology.
- Diving medicine (or hyperbaric medicine) is the prevention and treatment of diving-related problems.
- Evolutionary medicine is a perspective on medicine derived through applying evolutionary theory.
- Forensic medicine deals with medical questions in legal context, such as determination of the time and cause of death.
- Medical humanities includes the humanities (literature, philosophy, ethics, history and religion), social science (anthropology, cultural studies, psychology, sociology), and the arts (literature, theater, film, and visual arts) and their application to medical education and practice.
- eHealth, Medical informatics, and medical computer science are relatively recent fields that deal with the application of computers and information technology to medicine.
- Nosology is the classification of diseases for various purposes.
- Pharmacogenomics is a form of individualized medicine.
- PanVascular Medicine is an approach to deal with the problems of highly specialised but both, medical and economical inefficiently arranged human resources and medical equipment in today's vascular care facilities
- Sports medicine deals with the treatment and preventive care of athletics, amateur and professional. The team includes specialty physicians and surgeons, athletic trainers, physical therapists, coaches, other personnel, and, of course, the athlete.
- Therapeutics is the field, more commonly referenced in earlier periods of history, of the various remedies that can be used to treat disease and promote health
- Travel medicine or emporiatrics deals with health problems of international travelers or travelers across highly different environments.

Medical education

Medical education is education related to the practice of being a medical practitioner, either the initial training to become a physician or further training thereafter.

Medical education and training varies considerably across the world, however typically involves entry level education at a university medical school, followed by a period of supervised practice (Internship and/or Residency) and possibly postgraduate vocational training. Continuing medical education is a requirement of many regulatory authorities.

Various teaching methodologies have been utilised in medical education, which is an active area of educational research.

Legal restrictions

In most countries, it is a legal requirement for medical doctors to be licensed or registered. In general, this entails a medical degree from a university and accreditation by a medical board or an equivalent national organization, which may ask the applicant to pass exams. This restricts the considerable legal authority of the medical profession to physicians that are trained and qualified by national standards. It is also intended as an assurance to patients and as a safeguard against charlatans that practice inadequate medicine for personal gain. While the laws generally require medical doctors to be trained in "evidence based", Western, or Hippocratic Medicine, they are not intended to discourage different paradigms of health and healing, such as alternative medicine or faith healing.

Criticism

Criticism of medicine has a long history. In the Middle Ages, some people did not consider it a profession suitable for Christians, as disease was often considered God sent. God was considered to be the 'divine physician' who sent illness or healing depending on his will. However many monastic orders, particularly the Benedictines, considered the care of the sick as their chief work of mercy. Barber-surgeons (they had the sharpest knives) generally had a bad reputation that was not to improve until the development of academic surgery as a speciality of medicine, rather than an accessory field.

Through the course of the twentieth century, healthcare providers focused increasingly on the technology that was enabling them to make dramatic improvements in patients' health. The ensuing development of a more mechanistic, detached practice, with the perception of an attendant loss of patient-focused care, known as the medical model of health, led to further criticisms. This issue started to reach collective professional consciousness in the 1970s and the profession had begun to respond by the 1980s and 1990s.

Perhaps the most devastating criticism of modern medicine came from Ivan Illich. In his 1976 work Medical Nemesis, Illich stated that modern medicine only medicalises disease and causes loss of health and wellness, while generally failing to restore health by eliminating disease. This medicalisation of disease forces the human to become a lifelong patient.[3]Other less radical philosophers have voiced similar views, but none were as virulent as Illich. Another example can be found in Technopoly: The Surrender of Culture to Technology by Neil Postman, 1992, which criticises overreliance on technological means in medicine.

Criticism of modern medicine has led to some improvements in the curricula of medical schools, which now teach students systematically on medical ethics, holistic approaches to medicine, the biopsychosocial model and similar concepts.

The inability of modern medicine to properly address many common complaints continues to prompt many people to seek support from alternative medicine. Although most alternative approaches lack scientific validation, some may be effective in individual cases. The bioscience and alternative health care paradigms may differ to such an extent that what constitutes scientific evidence is contested. Many physicians practice alternative medicine

alongside "orthodox" approaches but the general body of medical practitioners is often criticised for ignoring the purported value of alternative medicine.

Medical errors are also the focus of many complaints and negative coverage. Practitioners of human factors engineering believe that there is much that medicine may usefully gain by emulating concepts in aviation safety, where it was long ago realized that it is dangerous to place too much responsibility on one "superhuman" individual and expect him or her not to make errors. Reporting systems and checking mechanisms are becoming more common in identifying sources of error and improving practice.

Radical critics of certain medical traditions may hold that whole fields or traditions of medicine are intrinsically harmful or ineffective. They would reject any use or support of practices belonging to that tradition. However, generally, there is a spectrum of efficacy on which all traditions lie; some are more effective, some are less effective, but nearly all contain some harmful practices and some effective ones. Naturally, though, most individuals or groups seeking a health care practice to improve their own health would seek a tradition with the maximum degree of efficacy. There is no doubt whatsoever that Western Allopathic medicine, together with its cohorts of improved hygiene and nutrition, have been collectively responsible for most of the improvements in health worldwide over the last century or so, including: increasing longevity, decreased child mortality, increasing population numbers, better ability to monitor and halt disease spread and outbreaks, improved access to health care for all strata of society.

See also

- Health
- Pharmaceutical company

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2. ^ Coulehan JL, Block MR (2005). The Medical Interview: Mastering Skills for Clinical Practice, 5th ed., F. A. Davis. ISBN 0-8036-1246-X.
3. ^ Ivan Illich (1976). Medical Nemesis. ISBN 0-394-71245-5 ISBN 0-7145-1095-5 ISBN 0-7145-1096-3.

Drugs

A *drug* is any biological substance, synthetic or non-synthetic, that is taken for non-dietary needs. It is usually synthesized outside of an organism, but introduced into an organism to produce its action. That is, when taken into the organisms body, it will produce some effects or alter some bodily functions (such as relieving symptoms, curing diseases or used as preventive medicine or any other purposes).

Note that natural endogenous biochemicals (such as hormones) can bind to the same receptor in the cell, producing the same effect as a drug. Thus, drug is merely an artificial definition that distinguishes whether that molecule is synthesized within an organism or outside an organism. For instance, insulin is a hormone that is synthesized in the body; it is considered as a hormone when it is synthesized by the pancreas inside the body, but if it is introduced into the body from outside, it is considered as a drug.

It is a substance which is not food,[1] and which, when ingested, affects the functioning of the mind, or the body, or both. However, under the philosophy of Chinese medicine, food is also considered a drug as it affects particular parts of body and cures some diseases. Thus, food does satisfy the above definition of drug so long as ingestion of it would alter some bodily functions.

Drugs used as medicines

Main article: Medication

A medication is a drug taken to cure or reduce symptoms of an illness or medical condition, or may use as preventive medicine that has future benefits but does not treat any existing or pre-existing diseases or symptoms. Dispensing of medication is often regulated by the government into three categories -- over the counter (OTC) medications, which are available in pharmacies and and supermarket's without special restrictions, behind the counter (BTC), which are dispensed by a pharmacist without needing a doctor's prescription, and Prescription only medicines (POM), which must be prescribed by a licensed medical professional, usually a physician.

Most OTC medications are generally considered to be safe enough that most people will not hurt themselves if they are taken as instructed. In UK, BTC medicine is called pharmacy medicines which can only be sold in registered pharmacies, by or under the supervision of a pharmacist. However, the precise distinction between OTC and prescription depends on the legal jurisdiction.

Medications are typically produced by pharmaceutical companies and are often patented to protect their exclusive rights to produce them, but they can also be derived from naturally occurring substance in plants called herbal medicine. Those that are not patented (or with expired patents) are called generic drugs since they can be produced by other companies without restrictions or licenses from the patent holder.

Recreational drugs

Recreational drug use is the use of psychoactive drugs for recreational purposes rather than for work, medical or spiritual purposes. Much controversy has arisen over recreational drug use, and governments across the world have regulated the consumption and/or distribution of drugs in the name of fighting drug abuse, but many countries' laws are criticised for being passed under ulterior motives or for being hypocritical.

List of drugs

See list of drugs for an alphabetical list of drugs by name. Many drugs have more than one name and, therefore, the same drug may be listed more than once. Brand names and generic names are differentiated by the use of capital initials for the former.

Footnotes

1. ^ Some substances, such as beers, wines, and some fungi, are sometimes regarded as both foods and drugs

See also

- Medication
- Prescription drug
- Psychoactive drug

Drug diversion

In the terminology of the Drug Enforcement Administration, *diversion* is the use of prescription drugs for recreational purposes. The term comes from the "diverting" of the drugs from their original purposes.

note: Drug Diversion may also refer to programs available to first time drug law infractors which "divert" them from the criminal system to a program of education and rehabilitation.

Drugs that are diverted, in an approximate order of popularity

- Opioids (opium analogues) such as hydrocodone and OxyContin. These have similar effects to opium and heroin.
- Pseudoephedrine-containing drugs sold over the counter are used as an ingredient to make methamphetamine.

- DXM, the active ingredient of Robitussin, is abused for its effects which are similar to Ketamine and PCP.
- Depressants such as Valium.
- Antidepressants, which are often essentially stimulants, and are often snorted by abusers.

The DEA is doing some work to try and stop drug diversion. For example, sales of Pseudoephedrine are limited in certain stores.

Some critics feel that the importance of drug diversion is glossed over in the media and popular discussion. For example, in the recent case of Rush Limbaugh being accused of abusing pain-killers, it was felt by some that the similarity between the pain killers and heroin was not made clear. The higher dose pills of prescription pain killers are often stronger than the street rock heroin sold in most cities, and are preferred or at least used indiscriminately by opiate drug abusers.

Some critics contend however that drug diversion has been purposely allowed to happen, primarily by opioid manufacturers who profit off of the addiction of their customers. They also point to new products such as "dex-alone" which is a pill marketed specifically that it contains pure DXM without other compounds which would have an adverse effect at the levels of abuse.

Registration of drug suppliers

21 U.S.C. § 822 of the Controlled Substances Act provides for registration of manufacturers and distributors of Scheduled substances. The criteria for registering manufacturers of Schedule I and II drugs are particularly strict and call for "limiting the importation and bulk manufacture of such controlled substances to a number of establishments which can produce an adequate and uninterrupted supply of these substances under adequately competitive conditions for legitimate medical, scientific, research, and industrial purposes". The Attorney General must make a positive determination that the registration would be "consistent with the public interest".

For manufacturers of other drugs, and for drug distributors, the regulations are substantially less strict: "The Attorney General shall register an applicant . . . unless he determines that the issuance of such registration is inconsistent with the public interest". The criteria for both manufacture and distribution is somewhat biased in favor of established industries, favoring "past experience" and a record of compliance with drug laws[1].

References

- Controlled Substances Act - U.S. Drug Enforcement Administration

Drug overdose

A *drug overdose* occurs when a drug is ingested in quantities and/or concentrations large enough to overwhelm the homeostasis of a living organism, causing severe illness or death. It is a type of poisoning.

Types

The word "overdose" implies that there is a safe dosage and therefore the term overdose is commonly only applied to drugs, not poisons.

Drug overdoses are sometimes caused intentionally to commit suicide, but many drug overdoses are accidental and are usually the result of either irresponsible behavior (such as overindulging at a party), or the misreading of product labels. Other causes of overdose (especially heroin) include multiple drug use with counter indications (cocaine/amphetamines/alcohol) or use after a period of abstinence.

A common unintentional overdose in young children involves multi-vitamins containing iron. Iron is a component of the hemoglobin molecule in blood, used to transport oxygen to living cells. When taken in small amounts, iron allows the body to replenish hemoglobin, but in large amounts it causes severe pH imbalances in the body. If this overdose is not treated with chelation therapy, it can lead to death or permanent coma.

Symptoms

Symptoms of overdose occur in various forms:

- Exaggerated form of normal action (sleepiness on antiepileptics, hypoglycemia on insulin)
- Other effects due to chemical properties of the medication (metabolic acidosis in aspirin, liver failure due to paracetamol)
- Non-specific symptoms due to central nervous system irritation (confusion, vertigo, nausea, vomiting)

Diagnosis

Diagnosis of an overdosed patient is generally straightforward if the drug is known. However, it can be very difficult if the patient cannot (or refuses to) state what drug they have overdosed on. At times, certain symptoms and signs exhibited by the patient, or blood tests, can reveal the drug in question. Even without knowing the drug, most patients can be treated with general supportive measures.

In some instances, empirical antidotes may be administered if there is sufficient indication that the patient has overdosed on a particular type of medication: naloxone in opioids and flumazenil in benzodiazepines. Rapid reversal of symptoms may serve as proof in these cases.

First aid

Medical disclaimer

Depressants

First aid can prevent a death from overdose of depressants as it may take several hours for someone to die in these cases. The common drugs in this category include opiates (ie. heroin, morphine and methadone), alcohol, and certain prescription drugs such as benzodiazepines. Signs of overdose are those of a depressed central nervous system — slow, infrequent or shallow breathing, blue lips or fingernails, cold or pale skin, slow or faint pulse, snoring or gurgling noises, and the inability to be woken from nodding off.

- The first step is to stay calm and see if you can get a response from the person by pinching the back of their arm, calling their name or rubbing your knuckles against their chest.
- If there is no response, check to make sure their airway is not blocked and see if they are breathing.
- See if they are breathing
- Roll them on to their side into the recovery position and perform cardiopulmonary resuscitation.[1]
- Call an ambulance. Ideally someone should call an ambulance immediately while another person evaluates the patient and attempts CPR. EMS personnel are not required by law to inform the police of drug overdoses, they usually do not inform the police as that would deter people from calling for help in an emergency.

Stimulants

People can overdose on stimulants, such as amphetamines, ecstasy and cocaine, too, with symptoms such as rapid heartbeat, muscle cramps, seizures, paranoia, psychosis, confusion, loss of control of movement, vomiting and lack of consciousness.

First aid in these cases involves staying with the person and helping them to remain calm. Move them to a quiet area, and where possible, apply a wet cloth to their neck or forehead. If unconscious, place them in the recovery position and call an ambulance.[1]

Prevention

- Be informed about any drugs you are taking.
- Do not take different types of illicit drugs together. [2]
- When you are unsure of a drug's strength, try a small dose first.
- Be aware of low tolerance following a period of abstinence (e.g. a period in detox or rehab or after leaving prison) when it comes to illicit drugs.

Causes

Common types of drugs that are overdosed on:

- Barbiturates

    - Seconal
    - Nembutal

- Narcotics
    - Heroin
- Stimulants
    - Cocaine
    - Methamphetamine
- Ethyl Alcohol
    - Alcoholic beverages
- Prescription drugs
    - drug "cocktails", or a combination of numerous drugs.

References

1. **^** a b Drugs first aid
2. ^ Mixing drugs

Drug resistance

Organisms are said to be *drug-resistant* when drugs meant to neutralize them have reduced effect. When an organism is resistant to more than one drug, it is said to be multidrug resistant. The most prominent example of this is antibiotic resistance. Drug resistance is also found in some tumor cells, which makes it more difficult to use chemotherapy to attack tumors made of those cells. When a drug such as an antibiotic is administered, those which have a genetic resistance to the drug will survive and reproduce, and the new population will be drug-resistant.

To counter drugs, bacteria and viral pathogens have evolved sophisticated mechanisms to inactivate these compounds (e.g. by pumping out compounds mutating residues required for the compound to bind etc.), and they do so at a rate that far exceeds the pace of new development of drugs. Examples include pan-drug resistant strains of Staphylococcus aureus, Klebsiella pneumonia, and Pseudomonas aerginosa, and Mycobacterium tuberculosis (TB) among bacterium and HIV-1 among viruses. Indeed, no new antibiotics have been developed against TB in thirty years. Efforts to develop new antibiotics by the

pharmaceutical industry by large-scale screens of chemical libraries which inhibit bacterial growth have largely failed, and new tetracycline and sulfanilamide analogs will likely engender resistance and will quickly be rendered useless. The resistance problem is compounded further by indiscriminate and inappropriate use of antibiotics and anti-viral compounds without compliance measures or public health policies to reduce disease burden. Finally, with current legislative restrictions, the astounding costs associated with clinical trials (e.g. ~$400M to bring new tetracyclines to market for an expected revenue of ~$100M), the failure to control generic sales, and the capacity to generate substantial revenues from medications for chronic illnesses, there is little if any financial incentive for big pharmaceutical companies to even develop new antibiotics, and small biotech companies simply do not have the resources. The search for novel anti-viral compounds has been somewhat more successful and largely motivated by the HIV pandemic, but drugs have been developed principally against viral targets, and mutation rates among viruses still outpaces new development. One positive development has been vaccines, which are promising for some bacterial and viral illnesses. But vaccines are not successful in all cases (e.g. in young children), and adequate resources have not been made available. In short, the lack of concerted effort by governments and the pharmaceutical industry, together with the innate capacity of microbes to develop resistance at a rate that outpaces development of new drugs, suggests that existing strategies for developing viable, long-term anti-microbial therapies are ultimately doomed to failure. Without alternative strategies, the acquisition of drug resistance by pathogenic microorganisms looms as possibly the single most significant public health threat facing humanity in the coming century.

Antipyretics

Antipyretics are drugs that prevent or reduce fever by lowering the body temperature from a raised state. However, they will not affect the normal body temperature if one does not have fever.

Antipyretics cause the hypothalamus to override an interleukin-induced increase in temperature. The body will then work to lower the temperature and the result is a reduction in fever.

Most are also used for other purposes. For example, the most common antipyretics in the United States are aspirin and acetaminophen, which are used primarily as pain relievers. There is some debate over the appropriate use of such medications: fever is part of the body's immune response to infection.

Herbal remedies with a fever-reducing effect are called *febrifuges*, and include catnip, chamomile, sage and yarrow. However, the term febrifuge can also refer to a refrigerant, such as topical alcohol, which cools the body by physically removing heat rather than modifying the body's responses.

Bisphosphonates

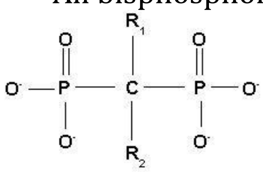
In pharmacology, *bisphosphonates* (also called: *diphosphonates*) is a class of drugs that inhibits the resorption of bone. Its uses include the prevention and treatment of osteoporosis, osteitis deformans ("Paget's disease of bone"), bone metastasis (with or without hypercalcemia), multiple myeloma and other conditions that feature bone fragility.

History

Bisphosphonates were developed in the 19th century, but were first investigated in the 1960s for use in disorders of bone metabolism. Their non-medical use included water softening in irrigation systems used in orange groves. The initial rationale for their use in humans was their potential in preventing the dissolution of hydroxylapatite, the principal bone mineral, and hence arresting bone loss. Only in the 1990s was their actual mechanism of action demonstrated.[1]

Chemistry and classes

All bisphosphonate drugs share a common P-C-P "backbone":



The two PO***3*** (phosphate) groups covalently linked to carbon determine both the name "bisphosphonate" and the function of the drugs.

The long side chain (*R*2 in the diagram) determines the chemical properties, the mode of action and the strength of bisphosphonate drugs. The short side chain (R***1***) mainly influences chemical properties and pharmacokinetics.

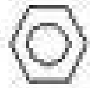
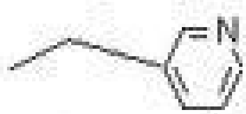
Pharmacokinetics

Of the bisphosphonate that is resorbed (from oral preparation) or infused (for intravenous drugs), about 50% is excreted unchanged by the kidney. The remainder has a very high affinity for bone tissue, and is rapidly absorbed onto the bone surface.

Mechanism of action

Bisphosphonates, when attached to bone tissue, are "ingested" by osteoclasts, the bone cell that breaks down bone tissue. The two types of bisphonates work differently in killing osteoclast cells.

There are two classes of bisphosphonate: the N-containing and non-N-containing bisphosphonates.

Agent	R_1 side chain	R_2 side chain
Etidronate	-OH	$-CH_3$
Clodronate	-Cl	-Cl
Tiludronate	-H	-S-  -Cl
Pamidronate	-OH	$-CH_2-CH_2-NH_2$
Neridronate	-OH	$-(CH_2)_5-NH_2$
Olpadronate	-OH	$-(CH_2)_2N(CH_3)_2$
Alendronate	-OH	$-(CH_2)_3-NH_2$
Ibandronate	-OH	$-CH_2-CH_2N$ $\langle$ CH_3 / $(CH_2)_4-CH_3$
Risedronate	-OH	
Zoledronate	-OH	

Non-nitrogenous

Non-N-containing bisphosphonates:

- Etidronate (Didronel®) - 1 (potency relative to that of etidronate)
- Clodronate (Bonefos®, Loron®) - 10
- Tiludronate (Skelid®) - 10

The non-nitrogenous bisphosphonates are metabolised in the cell to compounds that compete with adenosine triphosphate (ATP) in the cellular energy metabolism. The osteoclast initiates apoptosis and dies, leading to an overall decrease in the breakdown of bone.[2]

Nitrogenous

N-containing bisphosphonates:

- Pamidronate (APD, Aredia®) - 100

Neridronate - 100
Olpadronate - 500
Alendronate (Fosamax®) - 500
Ibandronate (Bondronat®) - 1000
Risedronate (Actonel®) - 2000
Zoledronate (Zometa®) - 10000

Nitrogenous bisphosphonates act on bone metabolism by binding and blocking the enzyme farnesyl diphosphate synthase (FPPS) in the HMG-CoA reductase pathway (also known as the mevalonate pathway).[3]

Disruption of the HMG CoA-reductase pathway at the level of FPPS prevents the formation of two metabolites (farnesol and geranylgeraniol) that are essential for connecting some small proteins to the cell membrane. This phenomenon is known as prenylation, and is important for proper sub-cellular protein trafficking (see "lipid anchored protein" for the principles of this phenomenon).[4]

While inhibition of protein prenylation may affect many proteins found in an osteoclast, disruption to the lipid modifcation of Ras, Rho, Rac proteins has been speculated to underlie the effects of bisphosphonates. These proteins can affect both osteoclastogenesis, cell survival, and cytoskeletal dynamics. In particular, the cytoskeleton is vital for maintaining the "ruffled border" that is required for contact between a resorbing osteoclast and a bone surface.

Statins are another class of drugs that inhibit the HMG-CoA reductase pathway. Unlike bisphosphonates, statins do not bind to bone surfaces with high affinity, and are thus not specific for bone. Nevertheless, some studies have reported a decreased rate of fracture (an indicator of osteoporosis) and/or an increased bone mineral density in statin users. The overall efficacy of statins in the treatment osteoporosis remains controversial.

Uses

Bisphosphonates are used clinically for the treatment of osteoporosis, osteitis deformans (Paget's disease of the bone), bone metastasis (with or without hypercalcemia), multiple myeloma and other conditions that feature bone fragility.

In osteoporosis and Paget's, alendronate and risedronate are the most popular first-line drugs. If these are ineffective or the patient develops digestive tract problems, intravenous pamidronate may be used. Alternatively, strontium ranelate or teriparatide are used for refractory disease, and the SERM raloxifene is occasionally administered in postmenopausal women instead of bisphosphonates.

High-potency intravenous bisphosphonates have shown to modify progression of skeletal metastasis in several forms of cancer, especially breast cancer.

More recently, bisphosphonates have been used to reduce fracture rates in children with osteogenesis imperfecta.

Side-effects

- Oral bisphosphonates can give stomach upset and inflammation and erosions of the esophagus, which is the main problem of oral N-containing preparations. This can be prevented by remaining seated upright for 30 to 60 minutes after taking the medication.
- Intravenous bisphosphonates can give fever and flu-like symptoms after the first infusion. Notably, these symptoms do not recur with subsequent infusions.
- There is a slightly increased risk for electrolyte disturbances, but not enough to warrant regular monitoring.
- In chronic renal failure, the drugs are excreted much slower, and dose adjustment is required.
- Bisphosphonates have been associated with osteonecrosis of the jaw; with the mandible twice as frequently affected as the maxilla and most cases occurring following high-dose intravenous administration used for some cancer patients. Some 60% of cases are preceded by a dental surgical procedure and it has been suggested that bisphosphonate treatment should be postponed until after any dental work to eliminate potential sites of infection.[5]
- A number of cases of severe bone, joint or musculoskeletal pain have been reported, prompting labeling changes[6]

Footnotes

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Dermatological preparations - Sunscreen

Sunscreen (also known as *sunblock*, *suntan lotion*) is a lotion, spray or other topical product that helps protect the skin from the sun's ultraviolet radiation, and which reduces sunburn and other skin damage, ultimately leading to a lower risk of skin cancer. However, suntan lotion is an incorrect term for sunscreen as it is something entirely different. Suntan lotion is used to attract UV rays in order to better tan where sunblock is used to deflect UV radiation. These are commonly called indoor tanning lotions when designed for use with tanning beds or just suntan lotion if designed for outdoor use and may or may not have SPF protection in them.

The best sunscreens protect against both UVB (ultraviolet radiation with wavelength between 290 and 320 nanometres), which can cause sunburn, and UVA (between 320 and 400 nanometres), which damages the skin with more long-term effects, such as premature skin aging. Most sunscreens work by containing either an organic chemical compound that absorbs ultraviolet light (such as oxybenzone) or an opaque material that reflects light (such as titanium dioxide, zinc oxide), or a combination of both. Typically, absorptive materials are referred to as chemical blocks, whereas opaque materials are mineral or physical blocks.

Dosing for sunscreen can be calculated using the formula for body surface area and subsequently subtracting the area covered by clothing. The dose used in FDA sunscreen testing is 2 mg/cm^2. From a sample calculation in a FDA monograph, if one assumes an "average" adult build of height 5 ft 4 in (163 cm) and weight 150 lb (68 kg) with a 32 in (82 cm) waist, that adult wearing a bathing suit covering the groin area should apply 29 g (approximately 1 oz) evenly to the uncovered body area.

Contrary to the common advice that sunscreen should be reapplied every 2–3 hours, research has shown that the best protection is achieved by application 15–30 minutes before exposure, followed by one reapplication 15–30 minutes after the sun exposure begins. Further reapplication is only necessary after activities such as swimming, sweating, and rubbing.[1]

However, more recent research at the University of California indicates that sunscreen needs to be reapplied within 2 hours in order to remain effective. Not reapplying could even cause more cell damage than not using sunscreen at all, due to the release of extra free radicals from the absorbed chemical.[2]

A significant reduction in sun exposure inhibits the production of vitamin D. However, excessive sun exposure has been conclusively linked to some forms of skin cancer and signs of premature aging. Recent studies have shown that vitamin D does not provide any protection from cancer. Season, geographic latitude, time of day, cloud cover, smog, skin type, and sunscreen all have an effect on vitamin D production in the skin, but fifteen minutes per day of direct exposure to the sun is a generally accepted guideline to follow for optimum vitamin D production. Experts generally recommend taking a fifteen minute walk in the morning or evening without wearing sunscreen to meet this requirement.

History

The ancient Greeks used olive oil as a type of sunscreen. However, this was not very effective. Throughout the early twentieth century, H.A. Milton Blake, a South Australian chemist, as well as several other inventors attempted to create an effective sunscreen but failed.

It was not until 1944 that the first effective sunscreen was invented. At that time, World War II was in full swing and many soldiers were getting serious sunburn. A pharmacist named Benjamin Greene decided to create something that would save the soldiers from the sun's harmful rays. In his wife's oven, he created a sticky, red substance which he called "red vet pet" (red veterinary petrolatum), which worked primarily by physically blocking the sun's rays with a thick petroleum-based product similar to Vaseline. Greene tested it on his own bald head. It did not work nearly as well as modern sunscreens, but it was a start.

Sunscreen has come a long way since its initial days. Modern products have much higher protection factors than Greene's sunscreen, and modern products can also be water- and sweat-resistant. But there are also negative effects. Some people rely too much on the product and do not understand the limitations of the sun protection factor (SPF); they assume that buying anything over SPF 30 will automatically prevent them getting burnt no matter how long they can stay in the sun. Too much sunbathing is one of the major causes of skin cancer across the world.

Addendum: An effective sunscreen had already been developed in 1938 by the Swiss chemistry student Franz Greiter, after he had severely burnt himself during an ascent of the Piz Buin on the border between Switzerland and Austria. He named his product, which he had developed in a small laboratory in his parents' home, Gletscher Creme or in English Glacier Cream. Still existing examples of the 'Glacier Cream' have shown to have a SPF of 2 and thus could be classed as an effective sunscreen.

Mechanism of action

The principal ingredients in sunscreens are usually aromatic molecules conjugated with carbonyl groups. This general structure allows the molecule to absorb high-energy ultraviolet rays and release the energy as lower-energy rays, thereby preventing the skin-damaging ultraviolet rays from reaching the skin. So, upon exposure to UV light, most of the ingredients (with the notable exception of avobenzone) do not undergo significant chemical change, allowing these ingredients to retain the UV-absorbing potency without significant photo-degradation.

Sun protection factor

The SPF (sun protection factor) of a sunscreen is a laboratory measure of the effectiveness of sunscreen; the higher the SPF, the more protection a sunscreen offers against UV-B (the ultraviolet radiation that causes sunburn) and UV-A (more associated with longer-term skin damage). The SPF indicates the time a person can be exposed to sunlight before getting sunburn with a sunscreen applied relative to the time he or she can be exposed

without sunscreen. For example, someone who would burn after 12 minutes in the sun would expect to burn after 2 hours (120 min) if protected by a sunscreen with SPF 10. In practice, the protection from a particular sunscreen depends on factors such as:

- The skin type of the user.
- The amount applied and frequency of re-application.
- Activities in which one engages (for example, swimming leads to a loss of sunscreen from the skin).
- Amount of sunscreen the skin has absorbed.

The SPF is an imperfect measure of skin damage because invisible damage and skin aging is also caused by the very common ultraviolet type A, which does not cause reddening or pain. Conventional sunscreen does not block UVA as effectively as UVB, and an SPF rating of 30+ may translate to significantly lower levels of UVA protection according to a 2003 study by RAFT trust-funded researchers. According to a 2004 study, UVA also causes DNA damage to cells deep within the skin, increasing the risk of malignant melanomas. Even some products labeled "broad-spectrum UVA/UVB protection" do not provide good protection against UVA rays [2]. The best UVA protection is provided by products that contain zinc oxide, avobenzone and mexoryl. Titanium dioxide probably gives good protection, but does not completely cover the entire UV-A spectrum[3].

Due to consumer confusion over the real degree and duration of protection offered, labeling restrictions are in force in several countries. In the United States in 1999, the Food and Drug Administration (FDA) decided to institute the labelling of SPF 30+ for sunscreens offering more protection, and a similar restriction applies in Australia. This was done to discourage companies making unrealistic claims about the level of protection offered (such as "all day protection"), and because an SPF over 30 does not provide significantly better protection

The SPF can be measured by applying sunscreen to the skin of a volunteer and measuring how long it takes before sunburn occurs when exposed to an artificial sunlight source. In the US, such an in vivo test is required by the FDA. It can also be measured in vitro with the help of a specially designed spectrometer. In this case, the actual transmittance of the sunscreen is measured, along with the degradation of the product due to being exposed to sunlight. In this case, the transmittance of the sunscreen must be measured over all wavelengths in the UV-B range (290–350 nm), along with a table of how effective various wavelengths are in causing sunburn (the erythemal action spectrum) and the actual intensity spectrum of sunlight (see the figure). Such in vitro measurements agree very well with in vivo measurements.

Mathematically, the SPF is calculated from measured data as

$$\mathrm{SPF} = \frac{\int A(\lambda)E(\lambda)d\lambda}{\int A(\lambda)E(\lambda)/\mathrm{MPF}(\lambda)\,d\lambda},$$

where E(») is the solar irradiance spectrum, A(») the erythemal action spectrum, and MPF(») the monochromatic protection factor, all functions of the wavelength ». The MPF is roughly the inverse of the transmittance at a given wavelength.

The above means that the SPF is not simply the inverse of the transmittance in the UV-B region. If that were true, then applying two layers of SPF 5 sunscreen would be equivalent to SPF 25 (5 times 5). The actual combined SPF is always lower than the square of the single-layer SPF.

The following are the FDA allowable active ingredients in sunblocks:

- p-Aminobenzoic acid (PABA) up to 15 %.

Avobenzone up to 3%.
Cinoxate up to 3%.
Dioxybenzone up to 3%.
Homosalate up to 15%.
Menthyl anthranilate up to 5%.
Octocrylene up to 10%.
Octyl methoxycinnamate (Octinoxate) up to 7.5%.
Octyl salicylate up to 5%.
Oxybenzone up to 6%.
Padimate O up to 8%.
Phenylbenzimidazole sulfonic acid (Ensulizole) up to 4%.
Sulisobenzone up to 10%.
Titanium dioxide up to 25%.
Trolamine salicylate up to 12 %.
Zinc oxide up to 25%.

Others include:

- 4-Methylbenzylidene camphor (USAN Enzacamene)

Tinosorb® M (USAN Bisoctrizole, INCI Methylene Bis-Benzotriazolyl Tetramethylbutylphenol)
Tinosorb® S (USAN Bemotrizinol, INCI Bis-Ethylhexyloxyphenol Methoxyphenyl Triazine)
Mexoryl® SX (USAN Ecamsule, INCI Terephthalylidene Dicamphor Sulfonic Acid)
Mexoryl® XL (INCI Drometrizole Trisiloxane)
Neo Heliopan® AP (INCI Disodium Phenyl Dibenzimidazole Tetrasulfonate)
Uvinul® A Plus (INCI Diethylamino Hydroxybenzoyl Hexyl Benzoate)
Uvinul® T 150 (INCI Octyl Triazone)
Uvasorb® HEB (INCI Diethylhexyl Butamido Triazone)
Parsol® SLX (INCI Polysilicone-15)

Most of these ingredients are not FDA approved, but all of them are approved within the EU. And some are permitted in other parts of the world as well. A lot of these relative new ingredients absorb UVA, making it easier for sunscreen manufacturers to formulate for the growing demand of sunscreens with better UVA protection.

Melanin

The hormone alpha-melanocyte stimulating hormone is made when the body is exposed to sunlight and is responsible for the development of the pigment melanin. Research is being

done to create stable artificial forms of the hormone. A promising candidate, melanotan, might be useful in the prevention of skin cancer, by causing tanning without the need for exposure to dangerous levels of UV.

Possible health effects

Recently, there has been increased attention to the possibility of adverse health effects associated with the synthetic compounds in most sunscreens. [5] A study published in April 1992, entitled "Could apples increase melanoma risk?" reported that the greatest increase in melanoma has occurred in those regions where sunscreen use is most prevalent.[4] Although one might believe that this effect is due to sunscreens being used more in regions where people are more exposed to UV light, this is not what is claimed by this study: Melanome incidence correlates strongly with the use of chemical sunscreens independently of the actual UV exposure.[5]

In a May 2006 report, "Nanomaterials, Sunscreens and Cosmetics: Small Ingredients, Big Risks", Friends of the Earth claimed that several types of nanoparticles (like titanium dioxide or zinc oxide) can be harmful to human tissue. Currently, there is no policy requiring mandatory product labelling on products that use these compounds.

Some individuals can have mild to moderate allergic reactions to certain ingredients in sunscreen, particularly the chemical benzophenone, which is also known as phenyl ketone, diphenyl ketone, or benzoylbenzene. It is not clear how much of benzophenone is absorbed into the bloodstream, but trace amounts can be found in urinalysis after use.

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3. ^ [1]
4. ^ Garland et al., "Could sunscreens increase melanoma risk?", Am. J. Public Health, *82*, 614 (1992)
5. ^ Hans R. Larsen, Sunscreens and Cancer, Int. J. Alternative and Complementary Med., *12*, 17 (1994)

Endothelin receptor antagonists

A *endothelin receptor antagonist* (*ERA*) is a drug which blocks endothelin receptors. Two main kinds of ERAs exist: selective (e.g. sitaxsentan), which affect endothelin A, and dual ERAs, which affect both endothelin A and B (e.g. bosentan)

Glycoprotein IIb/IIIa inhibitors

In* medicine*, a* glycoprotein IIb/IIIa inhibitors*, also* GpIIb/IIIa inhibitors*, is class of* antiplatelet agents*.

Several GpIIb/IIIa inhibitors exist:

- abciximab (ReoPro®)
- eptifibatide (Integrilin®)
- tirofiban (Aggrastat®)

Use

Glycoprotein IIb/IIIa inhibitors are frequently used during percutaneous coronary interventions (angioplasty with or without intracoronary stent placement).

They work by preventing platelet aggregation and thrombus formation. They do so by inhibition of the GpIIb/IIIa receptor on the surface of the platelets.

History

Their development arose from the understanding of Glanzmann's thrombasthenia, a condition in which the GpIIb/IIIa is lacking.[1]

Reference

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Ointments

An *ointment* is a viscous semisolid preparation used topically on a variety of body surfaces. These include the skin and the mucus membranes of the eye (an eye ointment), vagina, glans and nose. An ointment may or may not be medicated.

Related topical preparations include creams, lotions, liniments and gels.

Ointments generally are inexpensive to purchase.

Orphan drugs

The granting of the *orphan drug* status is designed to encourage the development of drugs which are necessary but would be prohibitively expensive/un-profitable to develop under normal circumstances.

In the United States, an orphan drug is any drug developed under the Orphan Drug Act of January 1983 ("ODA"), a federal law concerning rare diseases ("orphan diseases"), defined as diseases affecting fewer than 200,000 people in the United States or low prevalence is taken as prevalence of less than 5 per 10,000 in the community. This has been adopted as a subclause of the Food and Drug Administration (FDA) regulations. Because medical research and development of drugs to treat such diseases is financially disadvantageous, companies that do so are rewarded with tax reductions and marketing exclusivity, or a monopoly, on that drug for an extended time (twenty years). The concept behind the ODA is that the longer period of exclusivity will encourgage more companies to invest money in research. Under the act many drugs have been developed, including drugs to treat glioma, multiple myeloma, cystic fibrosis, and snake venom. In the US, from January 1983 to June 2004, a total of 1,129 different orphan drug designations have been granted by the Office of Orphan Products Development (OOPD) and 249 orphan drugs have received marketing authorisation in the US. In contrast, the decade prior to 1983 saw fewer than ten such products come to market.

A similar status exists in the European Union, administered by the Committee on Orphan Medicinal Products of the European Medicines Agency.

In 2003, the leading orphan drug by worldwide sales revenue was Amgen's Erythropoietin (Epogen®), with sales of $2.4bn.

Development of orphan drugs

Since few markets would naturally exist to create these goods, as the costs of developing, researching and producing this drug would likely exceed any revenues, government intervention is required, usually to establish such a market or to produce the goods itself. Critics of the free market often cite this as a market failure in free market economic systems. Free market advocates often respond that without government intervention development costs would be considerably lower.

The intervention by government can take a variety of forms:

- Tax benefits to companies who produce or research these drugs
- Granting of additional rights above and beyond those granted by the regular patent laws.
- Subsidizing and funding clinical research by universities and industry sponsors to develop medical products (including drugs, biological products, devices, and medical foods) for rare diseases.
- Creating a government-run company to research and produce drugs for an example of this type of solution).

See also

- Pharmaceutical company

Patent medicine

Patent medicine is the term given to various medical compounds sold under a variety of names and labels, though they were for the most part actually trademarked medicines, not patented. In ancient times, such medicine was called *nostrum remedium*, "our remedy" in Latin, hence the name "nostrum"; it is a medicine whose efficacy is questionable and whose ingredients are usually kept secret. The name patent medicine has become particularly associated with the sale of drug compounds in the nineteenth century under cover of colourful names and even more colourful claims. The promotion of patent medicines was one of the first major products of the advertising industry, and many advertising and sales techniques were pioneered by patent medicine promoters. Patent medicine advertising often talked up exotic ingredients, even if their actual effects came from more prosaic drugs. One memorable group of patent medicines — liniments that allegedly contained snake oil, supposedly a universal panacea — made snake oil salesman a lasting synonym for a charlatan.

Patent medicines and advertising

The phrase patent medicine comes from the early days of the marketing of medical elixirs, when those who found favour with royalty were issued letters patent authorising the use of the royal endorsement in advertising. The name stuck well after the American Revolution made these endorsements by the crowned heads of Europe obsolete. Few if any of the nostrums were actually patented; chemical patents came into use in the USA in 1925, and in any case attempting to monopolize a drug, medical device, or medical procedure was considered unethical by the standards upheld during the era of patent medicine.

Instead, the compounders of these nostrums used a primitive version of branding to distinguish themselves from the crowd of their competitors. Many familiar names from the era live on in brands such as Luden's cough drops, Lydia E. Pinkham's vegetable compound for women, Fletcher's Castoria, and even Angostura bitters, which was once marketed as a stomach remedy. Many of these medicines, though sold at high prices, were made from quite cheap ingredients. Their composition was well known within the pharmacy trade, and druggists would sell (for a slightly lower price) medicines of almost identical composition that they had manufactured themselves. To protect profits, the branded medicine advertisements laid great emphasis on the brand-names, and urged the public to accept no substitutes.

At least in the earliest days, the history of patent medicines is coextensive with the history of medicine itself. Empirical medicine, and the beginning of the application of the scientific method to medicine, began to yield a few effective herbal and mineral drugs for the physician's arsenal. These few tested and true remedies, on the other hand, were inadequate to cover the bewildering variety of diseases and symptoms. Beyond these patches of knowledge they had to resort to occultism; the "doctrine of signatures" — essentially, the application of sympathetic magic to pharmacology — held that nature had hidden clues to medically effective drugs in their resemblances to the human body and its parts. This led medical men to hope, at least, that, say, walnut shells might be good for skull fractures. Given

the state of the pharmacopoeia, and patients' demands for something to take, physicians began making "blunderbuss" concoctions of various drugs, proven and unproven. These concoctions were the ancestors of the several nostrums.

Touting these nostrums was one of the first major projects of the advertising industry. The marketing of nostrums under implausible claims has a long history. In Henry Fielding's Tom Jones (1749), allusion is made to the sale of medical compounds claimed to be universal panaceas:

As to Squire Western, he was seldom out of the sick-room, unless when he was engaged either in the field or over his bottle. Nay, he would sometimes retire hither to take his beer, and it was not without difficulty that he was prevented from forcing Jones to take his beer too: for no quack ever held his nostrum to be a more general panacea than he did this; which, he said, had more virtue in it than was in all the physic in an apothecary's shop.

Within the English-speaking world, patent medicines are as old as journalism. "Anderson's Pills" were first made in England in the 1630s; the recipe was allegedly learned in Venice by a Scot who claimed to be physician to King Charles I. The use of letters patent to obtain exclusive marketing rights to certain labelled formulas and their marketing fueled the circulation of early newspapers. The use of invented names began early. In 1726 a patent was also granted to the makers of "Dr. Bateman's Pectoral Drops"; at least on the documents that survive, there was no Dr. Bateman. This was the enterprise of a Benjamin Okell and a group of promoters who owned a warehouse and a print shop to promote the product.

A number of American institutions owe their existence to the patent medicine industry, most notably a number of the older almanacs, which were originally given away as promotional items by patent medicine manufacturers. Perhaps the most successful industry that grew up out of the business of patent medicine advertisements, though, was founded by William H. Gannett in Maine in 1866. There were few circulating newspapers in Maine in that era, so Gannett founded a periodical, Comfort, whose chief purpose was to propose the merits of Oxien, a nostrum made from the fruit of the baobab tree, to the rural folks of Maine. Gannett's newspaper became the first publication of the Gannett Corporation, whose flagship newspaper today is USA Today.

Another method of publicity undertaken mostly by smaller firms was the "medicine show," a travelling circus of sorts which offered vaudeville-style entertainments on a small scale, and which climaxed in a pitch for the nostrum being sold. Muscleman acts were especially popular on these tours, for this enabled the salesman to tout the physical vigour offered by the potion he was selling. The showmen frequently employed shills, who would step forward from the crowd and offer "unsolicited" testimonials about the benefits of the medicine for sale. Oftentimes, the nostrum was manufactured and bottled in the same wagon that the show travelled in. The Kickapoo Indian Medicine Company became one of the largest and most successful medicine show operators; their shows had an American Indian or Wild West theme, and employed many Native Americans as spokespeople. The medicine show lived on in American folklore and Western movies long after they had vanished from public meeting places.

Ingredients and their uses

What did the sellers claim as ingredients?

Some level of exoticism and mystery in the contents of the preparation was deemed desirable by their promoters. Unlikely ingredients such as the baobab fruit in Oxien were a recurring theme. A famous patent medicine of the period was Dr. Kilmer's Swamp Root; unspecified roots found in swamps had remarkable effects on the kidneys, according to its literature.

Native American themes were also useful; Natives, imagined to be noble savages, were thought to be in tune with Nature, and heirs to a body of traditional lore about herbal remedies and natural cures. One example of this approach from the period was Kickapoo Indian Sagwa, a product of the Kickapoo Indian Medicine Company of Connecticut (completely unrelated to the real Kickapoo Indian tribe of Oklahoma), supposedly based on a Native American recipe. This nostrum was the inspiration for Al Capp's "Kickapoo Joy Juice," featured in the comic strip, "Li'l Abner".

Other promoters took an opposite tack from timeless herbal wisdom. Just about any scientific discovery or exotic locale could be used as a key ingredient in a patent medicine. Consumers were invited to invoke the power of electromagnetism to heal their ailments. In the nineteenth century, electricity and radio were gee-whiz scientific advances that found their way into patent medicine advertising, especially after Luigi Galvani showed that electricity influenced the muscles. Devices meant to electrify the body were sold; nostrums were compounded that purported to attract electrical energy or make the body more conductive. Albert Abrams was a well known practitioner of electrical quackery, claiming the ability to diagnose and treat diseases over long distances by radio.

Towards the end of the period, a number of radioactive medicines, containing uranium or radium, were marketed. These apparently actually contained the ingredients promised, and there were a number of tragedies among their devotees; most notoriously, Eben McBurney Byers, a steel heir, a supporter of the popular radium water "Radithor", who contracted radium poisoning and had to have his jaw removed after taking more than a thousand bottles of "radium water." Water irradiators were sold that promised to infuse water placed within them with radon, which was thought to be healthy at the time.

What did they actually contain?

While various herbs, touted or alluded to, were talked up in the advertising, their actual effects often came from opium extracts, cocaine, or grain alcohol. Those containing opiates were at least effective in relieving pain, though they could result in addiction. This hazard was sufficiently well known that many were advertised as causing none of the harmful effects of opium (though many of those so advertised actually did contain opium) In the case of medicines for "female complaints", the principal "Female complaint" that the medicine was intended to treat was early pregnancy; such products contained ingredients capable of causing abortion, such as pennyroyal, tansy or savin.

Until the twentieth century alcohol was the most controversial ingredient; for it was widely recognised that the "medicines" could continue to be sold for their alleged curative properties even in prohibition states and counties. Many of the medicines were in fact liqueurs of various sorts, flavoured with herbs said to have medicinal properties. Peruna was a famous "Prohibition tonic," weighing in at around 18% grain alcohol. A nostrum known as "Jamaica ginger" was ordered to change its formula by Prohibition officials; to fool a chemical test, some vendors added a toxic chemical, cresyl phosphate, an organophosphate compound that had effects similar to a nerve agent. Unwary imbibers suffered a form of paralysis that came to be known as jake-leg. Some included laxatives such as senna or diuretics, in order to give the compounds some obvious medical effects. The narcotics and stimulants at least had the virtue of making the people who took them feel better, and in the eyes of the advertisers this was scored as a "cure."

Clark Stanley the "Rattlesnake King" produced Stanley's snake oil, publicly processing rattlesnakes at the World's Columbian Exposition in Chicago. His liniment, when seized and tested by the federal government in 1917, was found to contain mineral oil, 1% fatty oil, red pepper, turpentine and camphor. This is not too unlike modern capsaicin and camphor liniments.

When journalists and physicians began focusing on the narcotic contents of the patent medicines, some of their makers began substituting acetanilide, a particularly toxic non-steroidal anti-inflammatory drug, discovered in 1886, for the laudanum they used to contain. This ingredient change probably killed more of the nostrum's users than the narcotics did, since the acetanilide was toxic to the liver and kidneys.

What did they claim to be good for?

What were they supposed to be good for? Just about everything. Nostrums were openly sold that claimed to cure or prevent venereal diseases, tuberculosis, and cancer. Bonnore's Electro Magnetic Bathing Fluid claimed to cure cholera, neuralgia, epilepsy, scarlet fever, necrosis, mercurial eruptions, paralysis, hip diseases, chronic abscesses, and "female complaints." A panacea so universally effective cannot be bought today at any price. William Radam's Microbe Killer, a product sold widely on both sides of the Atlantic in the 1890s and early 1900s, had the bold claim 'Cures All Diseases' prominently embossed on the front of the bottle. Ebeneezer Sibley ('Dr Sibley') in late 18th and early 19th century Britain went so far as to advertise that his Solar Tincture was able to "restore life in the event of sudden death", amongst other marvels.

Every manufacturer published long lists of testimonials in which all sorts of human ailments were cured by the compounds. Fortunately for both their makers and users, the illnesses that they claimed were cured were almost invariably self-diagnosed, and the claims of the writers to have been healed of cancer or tuberculosis by the nostrum should be considered in this light. In fact many, if not most, patent medicines were products of quackery, and were of little or no therapeutic benefit.

The end of the patent medicine era

Muckraker journalists and other investigators began to publicize instances of death, drug addiction, and other hazards from the compounds. This took some small courage on behalf of the publishing industry that circulated these claims, since the typical newspaper of the period relied heavily on the patent medicines, which founded the U.S. advertising industry. In 1905, Samuel Hopkins Adams published an exposé entitled "The Great American Fraud" in Collier's Weekly that led to the passage of the first Pure Food and Drug Act in 1906. This statute did not ban the alcohol, narcotics, and stimulants in the medicines; it required them to be labelled as such, and curbed some of the more misleading, overstated, or fraudulent claims that appeared on the labels. In 1936 the statute was revised to ban them, and the United States entered a long period of ever more drastic reductions in the medications available unmediated by physicians and prescriptions.

The patent medicine makers moved from selling nostrums to selling deodorants and toothpastes, which continued to be advertised using the same techniques that had proven themselves selling nostrums for tuberculosis and "female complaints." One survival of the herbal exoticism that once characterized the patent medicine industry is the marketing of shampoos, which are often promoted as containing perfumes such as vetivert or ylang-ylang, and foods such as mangoes, bananas, or honey; consumers are urged to put these ingredients in their hair.

In more recent years, also, various herbal concoctions have been marketed as "nutritional supplements". While their advertisements are careful not to cross the line into making explicit medical claims, and often bear a disclaimer that asserts that the products have not been tested and are not intended to diagnose or treat any disease, they are nevertheless marketed as remedies of various sorts. Weight loss and similar claims are frequently found on these compounds. One of the most notorious such elixirs, however, calls itself "Enzyte", widely advertised for "natural male enhancement" — that is, penis enlargement. Despite being a compound of herbs, minerals, and vitamins, Enzyte formerly promoted itself under a fake scientific name Suffragium asotas. Enzyte's makers translate this phrase as "better sex," but it is in fact ungrammatical Latin for "refuge for the dissipated."[1]

Surviving consumer products from the patent medicine era

A number of brands of consumer products that date from the patent medicine era are still on the market and available today. Their ingredients may have changed from the original formulas; the claims made for the benefits they offer have typically been seriously revised. These brands include:

- 666 Cold Medicine

Absorbine Jr.
BC Powder
Bromo-Seltzer
Carter's Little Liver Pills (Currently sold as Carter's Little Pills)
Chlorodyne
Doan's Pills

Fletcher's Castoria
Geritol
Goody's Powder
Lobeila Cough Syrup
Luden's Throat Drops
Phillips' Milk of Magnesia
Lydia E. Pinkham's Vegetable Compound
Smith Brothers Throat Drops
Vicks VapoRub

A number of patent medicines are produced in China; among the best known of these is Shou Wu Chih, a black, alcoholic liquid which is claimed to turn gray hair black.

Products no longer sold under medicinal claims

Some consumer products were once marketed as patent medicines, but have been repurposed and are no longer sold for medicinal purposes. Their original ingredients may have been changed to remove drugs, such is the case with Coca-Cola. The compound may also simply be used in a different capacity, as in the case of Angostura Bitters, now associated chiefly with cocktails.

- Angostura Bitters

Bovril
Coca-Cola
Dr Pepper
Hires Root Beer
Moxie brand soda

- tonic water

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- The Golden Age of Quackery, Stewart A. Holbrook. (Boston: MacMillan & Co., 1959)
- The Great American Medicine Show, David and Elizabeth M. Armstrong, (New York, Prentice-Hall, 1991) ISBN 0-13-364027-2

Pyrazole

Chemical name Pyrazole

Chemical formula $C_3H_4N_2$

Synonyms 1,2 diazole, Pyrazol

Molecular mass 68.07 g/mol

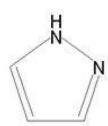
Melting point 66-70 °C

Boiling point 186-188 °C

Density x.xxx g/cm3

CAS number 288-13-1

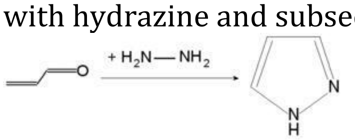
SMILES C1=CC=NN1



Disclaimer and references

Pyrazole refers both to the class of simple aromatic ring organic compounds of the heterocyclic series characterized by a 5-membered ring structure composed of three carbon atoms and two nitrogen atoms in adjacent positions and to the unsubstituted parent compound. Being so composed and having pharmacological effects on humans, they are classified as alkaloids although they are not known to occur in nature.

Pyrazoles are produced synthetically through the reaction of ±,^{2}-unsaturated aldehydes with hydrazine and subsequent dehydrogenation.



Pyrazoles are used for their analgesic, anti-inflammatory, antipyretic, antiarrhythmic, tranquilizing, muscle relaxing, psychoanaleptic, anticonvulsant, monoamineoxidase inhibiting, antidiabetic and antibacterial activities.

Structurally related compounds are pyrazoline and pyrazolidine.

Pyrazolopyrimidines

The *Pyrazolopyrimidines* are a class of nonbenzodiazepine drugs related (in terms of their effect) to benzodiazepines.

These drugs are intended to induce sleep, and are prescribed for people suffering insomnia.

They include:

- Zaleplon as Sonata ®

Indiplon ®

Insecticide

A related use is in pyrazolopyrimidine organothiophosphate insecticides.

Structure

The molecules are typified by the linked six sided (benzene) and sometimes five sided rings (methylpyrazol).

Drugs in sport

In sports, *doping* refers to the use of performance-enhancing drugs such as anabolic steroids, particularly those that are forbidden by the organizations that regulate competitions. Some doping substances, however, are permitted in low doses (alcohol and caffeine). Another form of doping is blood doping, either by blood transfusion or use of the hormone erythropoietin (EPO). Also considered "doping" by many is the use of substances that mask other forms of doping.

Currently, tetrahydrogestrinone (THG) and modafinil are causing controversy throughout the sporting world, with many high profile cases attracting major press coverage as prominent United States athletes have tested positive for these doping substances. Some athletes who were found to have used modafinil protested as the drug was not on the prohibited list at the time of their offence; however, the World Anti-Doping Agency (WADA) maintains it is a substance related to those already banned, so the decisions stand. Modafinil was added to the list of prohibited substances on August 3, 2004, ten days before the start of the 2004 Summer Olympics.

In recent years, gene doping has been reported as being an emerging form of doping. Gene doping would be very difficult to detect and when used it will last for many years.

Reaction from sports organizations

The International Amateur Athletic Federation, now the International Association of Athletics Federations, were the first international governing body of sport to take the situation seriously. In 1928 they banned participants from doping, but with little in the way of testing available they had to rely on the word of the athlete that they were clean.

It was not until 1966 that FIFA (soccer) and Union Cycliste Internationale (cycling) joined the IAAF in the fight against drugs, closely followed by the International Olympic Committee the following year.

Progression in pharmacology has always outstripped the ability of sports federations to implement rigorous testing procedures but since the creation of the World Anti-Doping Agency in 1999 more and more athletes are being caught.

The first tests for athletes were at the 1966 European Championships and two years later the IOC implemented their first drug tests at both the Summer and Winter Olympics. Anabolic steroids became prevalent during the 1970s and after a method of detection was found they were added to the IOC's prohibited substances list in 1976.

A handful of commentators maintain that as outright prevention of doping is an impossibility, and that all doping should be legalised. However, most disagree with this assertion, pointing out the harmful long-term effects of many doping agents. With doping legal, all competitive athletes would be compelled to use drugs, the net effect would be a level playing field but with widespread health consequences.

Another point of view is that doping could be legalized to some extent using a drug whitelist and medical counseling, such that medical safety is ensured, with all usage published. However, under such a system, it is likely that athletes would cheat by exceeding official limits to try to gain an advantage, policing such a system would be as difficult as policing a total ban on performance enhancing drugs.

Notable drug scandals and use in professional sport

The first recorded attempt to enhance performance occurred as early as the 8th century BC, when Ancient Greek Olympians ate sheep's testicles; today we would recognize these as a source of testosterone.

As early as the late 19th century professional cyclists were using substances like caffeine, cocaine and ether-coated sugar cubes to improve performance, reduce pain and delay fatigue.

In the 1904 Olympics, Thomas Hicks (USA) won the marathon at St. Louis and collapsed. It took hours to revive him; he had taken brandy mixed with strychnine to help him win his gold medal.

Nazi Germany athletes were rumored to use the first rudimentary testosterone preparations in the 1936 Summer Olympics.

World Weightlifting Championships of 1954 was the first unconfirmed testosterone injections by Soviet Athletes doping attempt ending in the Soviets winning the gold medal in most weight classes and breaking several world records.

In early 1960s Dr. John Ziegler (who was the US Team Coach in the 1954 Soviet-dominated World Weightlifting Championships) administered his weightlifters Dianabol tablets and the US dominated the 1962 World Championships.

In 1965 Dutch swimmers used stimulants.

During the 1967 Tour de France, Tom Simpson collapsed during the ascent of the Mont Ventoux. Despite mouth-to-mouth resuscitation and the administration of oxygen, plus a helicopter airlift to a nearby hospital, Simpson died. Two tubes of amphetamines and a further empty tube were found in the rear pocket of his racing jersey.

A famous case of illicit drug use in a competition was Canadian Ben Johnson's victory in the 100 m at the 1988 Summer Olympics. He subsequently failed the drug test when stanozolol was found in his urine. He later admitted to using the steroid as well as Dianabol, Cypionate, Furazabol, and human growth hormone amongst other things. Carl Lewis was then promoted one place to take the Olympic gold title. Later it was revealed that he also had been using drugs.

In the 1970s and 1980s, many athletes from Eastern bloc nations were suspected to be augmenting their ability with some kind of pharmacological help. After the fall of communism in Eastern Europe and the reunification of Germany, documents surfaced proving that the East German sport establishment had conducted systematic doping of virtually all of its world-class athletes.

In 1998 the entire Festina team were excluded from the Tour de France following the discovery of a team car containing large amounts of various performance-enhancing drugs. The team director later admitted that some of the cyclists were routinely given banned substances. Six other teams pulled out in protest including Dutch team TVM who left the tour still being questioned by the police. The Festina scandal overshadowed cyclist Marco Pantani's tour win, but he himself later failed a test. More recently David Millar, the 2003 World-Time Trial Champion, admitted using EPO, and was stripped of his title and suspended for two years. Still later, Roberto Heras was stripped of his victory in the 2005 Vuelta a España and suspended for two years after testing positive for EPO.

In July 2005, founders of California's Bay Area Laboratory Co-operative pleaded guilty to steroid distribution and money laundering. Those implicated or accused in the ensuing scandal include athletes Dwain Chambers, C.J. Hunter, Marion Jones and Tim Montgomery, baseball players Barry Bonds, Jason Giambi and Gary Sheffield, and several members of the Oakland Raiders.

At the 2006 Winter Olympics, Walter Mayer fled from the police when, acting on a tip, the Italian authorities conducted a surprise raid to search for evidence of doping.

The 2006 book Game of Shadows alleges extensive use of several types of steroids and growth hormone by baseball superstar Barry Bonds, and also names several other athletes as drug cheats.

In 2006, Spanish police arrested five people, including the sporting director of the Liberty Seguros cycling team, on charges of running a massive doping scheme involving most of the team and many other top cyclists. Several potential contenders in the 2006 Tour de France were forced to withdraw when they were linked to the scheme. For more details, see Operación Puerto doping case.

Less than a week after the 2006 Tour de France it was revealed that winner Floyd Landis had tested positive for an elevated testosterone/epitestosterone ratio (with normal levels of testosterone and deficient levels of epitestosterone) after his stunning stage 17 victory. Secondary tests have also confirmed the preliminary findings of deficient levels of epitestosterone resulting in a skewed T/E ratio, and a decision to strip him of the title is currently pending.

On July 29, another American champion failed a drug test - Olympic and world 100-meter champion Justin Gatlin.

In September 2006, Some former teammates of Cyclist Lance Armstrong admitted to taking EPO during the 1999 Tour de France. While they did not state that Armstrong had done the same, the article printed did attack Armstrong, who throughout his carrer has been a target of doping alligations, mainly stemming from his recovery from cancer and eventually winning a record seven straight Tour de France titles.

For a full discussion on the collective bargaining clauses in the four major North American sports relating to steroids testing and detection, see "Illegal Muscle- A Comparative Analysis of Proposed Steroid Legislation and the Policies in Professional Sports'

CBA's That Led to the Steroid Controversy. Paul A. Fortenberry and Brian E. Hoffman. 5 Va. Sports & Ent. L.J. 121 (2006)

MLB players accused of doping

- José Canseco (admitted to use of steroids)
Mark McGwire STL
Juan Gonzalez CLE
Mike Piazza SD
Iván Rodríguez DET
Miguel Tejada BAL
Roger ClemensHOU
Barry Bonds SF
Sammy Sosa BAL
Brett Barclay TOR
Rafael Palmeiro BAL (tested positive for stanozolol)
Andy Pettitte HOU
Brian Roberts BAL
Jay Gibbons BAL
Jason Giambi NYY
Ken Caminiti HOU (admitted to use of steroids)
Curt Schilling BOS
Dave Martinez
Tony Saunders
Wilson Alvarez
Bret Boone
Brady Anderson
Jason Grimsley ARI (admitted to use of several performance-enhancers)
Gary Sheffield NYY
Jeremy Giambi

Sympathomimetics

Sympathomimetics are a class of drugs whose effects mimic those of a stimulated sympathetic nervous system. As such they increase cardiac output, dilate bronchioles, and usually produce constriction of blood vessels. Sympathomimetics include the naturally occurring substances such as adrenaline (epinephrine), noradrenaline (norepinephrine), dopamine, ephedrine, and cocaine, as well as the synthetic drugs pseudoephedrine, phenylephrine, phenylpropanolamine, Amphetamine and methamphetamine, among others.

In medicine, certain sympathomimetics are commonly prescribed in cardiac emergencies including shock, asthma and anaphylaxis, in some cases for weight loss, and in cold remedies, where they shrink swollen membranes in the upper respiratory tract.

In recent years, phenylpropanolamine has been removed from over-the-counter cold formulations after it was implicated in causing an increased risk of hemorrhagic stroke.

See also

- Parasympathomimetics

Tocolytics

Tocolytics are medications used to suppress premature labor (toco refers to contractions, and lytic to removal). They are nearly always given in midpregnancy during preterm labor, when delivery would result in an extremely premature infant. This therapy is mainly instituted so that administration of glucocorticoids (which accelerate fetal lung maturity) can begin.

During administration of tocolytic medications, the mother's condition and the fetal heart rate pattern will be closely monitored by a health care professional to determine effects the medication is having on the mother and fetus' well being. If medication as well as other interventions fail to have the desired effect, immediate cesarian delivery may be required. Tocolytic therapy can delay birth by up to several days at its best.

Types of agents

Various types of agents are used, with varying success rates and side effects. Some medications are not FDA approved specifically for use in stopping uterine contractions in preterm labor, but are still used off label. Magnesium sulfate is the most commonly used tocolytic agent.

Examples:

- $MgSO_4$
  - Ritodrine (Yutopar)

  Fenoterol
  Nifedipine (Procardia, Adalat)
  Atosiban
  Indomethacin
  Terbutaline (Brethine)

Ethyl alcohol was frequently prescribed as a tocolytic in the mid-20th century, but later double-blind studies[1] have not shown it to be effective.

Contraindications to Tocolysis

Several factors may contraindicate delaying birth with the use of tocolytic medications. [2]

- Fetus is older than 37 weeks gestation

Fetus weighs more than 2500g or has IUGR
Fetus is in acute distress or has passed (or has a fatal anomaly)
Dilation is greater than 4 cm
Chorioamnionitis or intrauterine infection is present
Mother has severe PIH, eclampsia, active vaginal bleeding, a cardiac disease, or another condition which indicates that the pregnancy should not continue.

References

1. Castren O, Gummerus M, Saarikoski S. Treatment of imminent premature labour. Acta Obstet Gynecol Scand 1975;54:95–100.
1. Wong, Perry, and Hockenberry. Maternal Child Nursing Care. Mosby 2002

Triptans

Triptans are a family of tryptamine drugs used as abortive medication in the treatment of migraine and cluster headaches. They were first introduced in the 1990s. While effective at treating individual headaches, they are neither a preventative nor a cure. Their action is attributed to their binding to serotonin 5-HT1B and 5-HT1D receptors in cranial blood vessels (causing their constriction) and subsequent inhibition of pro-inflammatory neuropeptide release.

A test measuring a person's skin sensitivity during a migraine may indicate whether the individual will respond to treatment with triptans. Triptans are most effective in those with no skin sensitivity; with skin sensitivity, it is best to take triptans within twenty minutes of the headache's onset.

Triptans include sumatriptan (Imitrex, Imigran), rizatriptan (Maxalt), naratriptan (Amerge, Naramig), zolmitriptan (Zomig), eletriptan (Relpax), almotriptan (Axert, Almogran), and frovatriptan (Frova, Migard).

References

- Tepper S. J., Rapoport A. M. (1999). "The triptans - A summary". CNS Drugs *12* (5): 403-417.

Vasodilators

Vasodilation is where blood vessels in the body become wider following the relaxation of the smooth muscle in the vessel wall. This will reduce blood pressure - since there is more room for the blood. The opposite physiological process is vasoconstriction.

Vasomotor refers to the muscles and nerves controlling the process of vasodilation.

A *vasodilator* is a substance that causes vasodilation. Several vasodilators are used as drugs which may, for example, allow blood to flow more easily around a clot.

Flushing may be a physiological response to vasodilators.

Natural vasodilators and Drugs that Exploit Them

- Absence of high levels of environmental noise

- Adenosine
  - Adenocard - this is primarily used as an anti-arrhythmic.
- Adrenaline and noradrenaline vasodilate arterioles of the skeletal muscles. (By acting on beta-2 adrenergic receptors.) These chemicals cause vasoconstriction elsewhere.
  - Alpha blockers (block the constricting effect of adrenaline).
- L-Arginine

Atrial natriuretic peptide (ANP) - a weak vasodilator.
Bradykinin
Endothelium-derived hyperpolarizing factor (EDHF)

- Histamine
  - Complement proteins C3a, C4a and C5a work by triggering histamine release from mast cells and basophil granulocytes.
- Niacin (aka nicotinic acid)
- Nitric oxide
  - Glyceryl trinitrate (commonly known as Nitroglycerin)
  Isosorbide mononitrate & Isosorbide dinitrate
  Pentaerythritol Tetranitrate (PETN)
  Sodium nitroprusside
  - PDE5 inhibitors: these agents indirectly increase the effects of nitric oxide
    - Sildenafil
    - Tadalafil
    Vardenafil
- Platelet activating factor (PAF)

Prostacyclin (PGI2) as well as other prostaglandins.

- Tetrahydrocannabinol (THC) - the major active chemical in marijuana. Its mild vasodilating effects redden the eyes of cannabis smokers.
- Papaverine an alkaloid found in the opium poppy papaver somniferum

Erythropoietin (Procrit)

Identifiers

Symbol(s) EPO

Entrez 2056

OMIM 133170

RefSeq **NM_000799**

UniProt P01588

Other data

Locus Chr. 7 q21

Erythropoietin (IPA pronunciation: [jÌyj¸.yoÈpo.j.tjn], alternative pronunciations: [jÌrj¸roŠÈpTjtn, YÌrj¸roŠ-, YÌri¸roŠ-]) or *EPO* is a glycoprotein hormone that is a cytokine for erythrocyte (red blood cell) precursors in the bone marrow. Also called hematopoietin or hemopoietin, it is produced by the kidney, and is the hormone regulating red blood cell production. Erythropoietin is available as a therapeutic agent produced by recombinant DNA technology in mammalian cell culture. It is used in treating anemia resulting from chronic renal failure or from cancer chemotherapy. Its use is also believed to be common as a blood doping agent in endurance sports such as bicycle racing, triathlons and marathon running.

Discovery and biological role

The existence of a humoral factor regulating red blood cell production was first postulated in 1906 based on transfusion experiments in rabbits. In 1950, the still unidentified erythropoietic factor was found to be stimulated in rats breathing a low-oxygen atmosphere, thus establishing the elements of its biological regulation. In the 1960s its source was identified as the kidneys. Human EPO was first purified from human urine by T. Miyake, C. K. Kung and E. Goldwasser at the University of Chicago in 1977. Limited quantitites of the native human protein were used experimentally to treat patients with anemia.

EPO has now been identified as a glycoprotein with a molecular mass of about 30,000 Daltons. It has a 165 amino acid chain with four oligosaccharide side chains and circulates in the blood plasma at a very low concentration (about 5 pmol/L).

In adult humans, EPO is produced primarily by peritubular cells in the kidneys, where its production is stimulated by low oxygen levels in the blood, also known as hypoxia. Some EPO is also produced by the liver, which is the primary source in the fetus.

EPO acts by binding to a specific erythropoietin receptor (EpoR) on the surface of red cell precursors in the bone marrow, stimulating them to transform into mature red blood cells. As a result the oxygen level in blood reaching the kidney rises and the amount of EPO produced decreases.

Because the kidneys are the primary source of erythropoietin, chronic kidney disease often results in a systemic deficiency of EPO and consequent anemia. Anemia can also occur in cancer patients, sometimes as a direct result of the malignancy but usually as an adverse effect of chemotherapy.

Also, in patients who may require a blood transfusion or undergo surgery where blood loss is expected, EPO is given in advance as a precaution. The bone marrow produces more red blood cells, and if blood is lost during the operation, there is still enough to sustain the patient.

EPO as a therapeutic agent

Therapeutic human erythropoietin was initially isolated and purified from urine in 1977. In 1983, the gene coding for erythropoietin was identified by a team headed by Fu-Kuen Lin at U.S. biotechnology company Amgen. Researchers at The Genetics Insitute (now part of Wyeth) independently discovered the gene at approximately the same time. The resulting patent dispute led to Amgen gaining exclusive marketing rights for erythropoietin in the U.S. Recombinant DNA technology was used to express the protein in Chinese hamster ovary cells, which allowed a synthetic form of EPO (rEPO) to be produced in commercial quantities for the first time.

Recombinant EPO was launched as a pharmaceutical product by Amgen for treatment of anemia resulting from chronic renal failure in 1989 under the brand name Epogen. In 1991 it was also approved for treating anemia resulting from cancer chemotherapy. However, recent clinical studies on patients with head and neck squamous cell carcinoma (HNSCC) and breast carcinoma, in addition to relevant basic science research have demonstrated that patients whose tumors are positive for the erythropoietin receptor (EpoR) may be at increased risk of tumor progression (metastatic spread) if treated with Epo. Johnson & Johnson (J&J), an American pharmaceutical company, markets EPO under license from Amgen for cancer chemotherapy under the brand name Procrit. Amgen's patents have so far prevented other companies from entering the U.S. market. Even though the patents are all based on work done in the early 1980s, the last of them will not expire until 2015, thirty-two years after the date of the original application.

A longer-acting erythropoietin analogue, darbepoetin (dEPO), also known as novel erythropoiesis-stimulating protein (NESP), was launched by Amgen under the brand name Aranesp in 2001. Relative to rEPO, dEPO has a slightly different amino acid sequence and a greater number of oligosaccharide residues. Aranesp comes in 40mcg and 60mcg 1mL vials, and 100mcg and 200mcg prefilled syringes. It's primary advantage is it can be used only once every two weeks in patients without ESRD (end-stage renal disease).

Outside the U.S. Amgen's patents did not prevail and two other brands of EPO are available: Eprex (J&J) and NeoRecormon. (Roche). Two new long-acting forms may be launched in Europe in 2006: CERA (Roche) and Dynepo (Shire)

EPO is generally injected subcutaneously (under the skin) by the patient, although it may also be given intravenously. Several injections weekly are required for the original forms, but the long-acting forms may require injections only once every two weeks. EPO cannot be used by patients with leukemia and should be used cautiously by patients with uncontrolled high blood pressure. An extremely rare but severe adverse effect of EPO is acquired pure red cell aplasia (PRCA), an auto-immune condition in which the bone marrow loses its ability to produce red blood cells, leaving the patient dependent on blood transfusions. Certain lots of the J&J Eprex product were associated with a higher incidence of this problem. Studies at J&J showed that the PRCA was caused by interaction of EPO protein with a rubber compound in the pre-filled syringe used to distribute the product. Substitution of a teflon-coated syringe plunger eliminated the problem. By far the most common side-effect for any EPO products is fever. Also, use of EPO products can lead to an increased chance of the formation of blood clots (see below). Headache, nausea, vomiting, and delerium are also common side-effects.

These generally subside after 2-3 days. Fever lasting longer than 3 days or rising above 103 degrees Fahrenheit (39.5 °C) should be reported to your physician immediately. Concomminant use of aspirin with EPO products is encouraged to reduce the chance of clotting.

All forms of recombinant erythropoeitin are expensive. A dialysis patient, who can expect to require lifelong EPO treatment, will pay up to $10,000 per year for the drug in the U.S. Cancer chemotherapy patients, who require EPO for shorter periods, pay about $1,000 per month in the U.S. Worldwide revenues for sales of EPO were over USD$10 billion in 2004[1].

Erythropoietin as a blood doping agent

Although pharmaceutical EPO has benefited many thousands of anemic patients, it also has a converse side as a blood doping agent sometimes used by healthy athletes to gain a competitive advantage. By increasing the oxygen-carrying capacity of the blood it increases the aerobic respiratory capacity of the muscles, making it appealing to participants in endurance sports such as cycling and long-distance running. It is considered to be especially valuable in multi-stage bicycle races, where it can offset the decrease in red blood cells that occurs over several weeks of racing.

EPO doping probably became common in Grand Tour cycling after pharmaceutical EPO became available in the late 1980s, but there was at the time no way to prove its use in the absence of physical evidence of EPO possession. In retrospect, the deaths of a dozen or more elite cyclists in the early 1990s from heart failure while sleeping, were grim evidence of its overuse.

Excessive use of pharmaceutical EPO can lead to so many red blood cells that the blood becomes thick enough to strain the heart, especially during sleep when the heart rate is low. Beyond a certain point, the increase in haematocrit is actually detrimental to the oxygen carrying capacity due to negative haemodynamic effects, and increases the likelihood of developing symptoms similar to chronic mountain sickness.

The extent of the doping problem became undeniable after the Festina team scandal in the 1998 Tour de France, in which Willy Voet, a soigneur for the team, was apprehended with a huge cache of doping materials, including EPO. He[2] and others[3] later wrote about the widespread use of drugs in cycling.

In the wake of the Festina affair, the Union Cycliste Internationale (UCI) sought to limit EPO doping by testing riders' red blood cell concentrations as measured by hematocrit(HCT), the proportion by volume of blood cells that are red blood cells. A normal HCT in adult men is 41-50%. Under the UCI rule, any rider with a HCT over 50% was temporarily banned from racing. An independent organization, the World Anti-Doping Agency (WADA), was also created.

The response of EPO-doping athletes has been to monitor their HCT using portable blood centrifugation equipment and engineer their use of pharmaceutical EPO to maintain a HCT of just under 50%. When necessary, blood-thinning infusions are used to reduce HCT to a legal level, ideally 49.9%. Team management, doctors and coaches have in some cases been accused of complicity.

In the 2000 Tour de France, a laboratory test to detect residues of pharmaceutical EPO in urine was introduced for the first time as an anti-doping measure. It was developed by the

French National Laboratory for Doping Detection (LNDD). The test method relies on laboratory methods for distinguishing pharmaceutical EPO from the endogenous EPO normally present in an athlete's urine after strenuous exercise. Because existing brands of pharmaceutical EPO are made in cultured animal cells, they have a different pattern of oligosaccharide residues than the native human form.

Although widely applied, the test is controversial. In 2005, Rutger Beke, a Belgian triathlete successfully challenged his conviction for EPO doping by presenting scientific evidence that the test was unreliable in his case. Several other athletes have since made similar defenses. In the highest profile case to date, Spanish rider Roberto Heras was stripped of what would have been his fourth win of the Vuelta a España in 2005 after a positive urine test for pharmaceutical EPO. He has asserted his innocence and vowed to challenge the conviction based on the handling of his sample and alleged weaknesses in the test method.

If Dynepo becomes available as a pharmaceutical product in 2006 as expected, it may be a boon to doping athletes. It is to be manufactured in cultured human cells and should thus have an authentic pattern of human glycosylation, making it undetectable by the current test method.

Erythropoietin and Jehovah's Witnesses

Jehovah's Witnesses believe that they are to "abstain from blood"; this belief results in the refusal to accept transfusions of blood or blood components.

The use of erythropoietin to increase the number of red blood cells is one suggested alternative to a blood transfusion.

However, the presence of human albumin in the erythropoietin mixture may preclude its use in some Jehovah's Witnesses.

References

1. ^ See http://www.i-s-b.net/business/rec_sales.htm Info Service Biotechnology; Sales of Recombinant Drugs.
2. ^ Willy Voet, Massacre à la chaîne.
3. ^ Christophe Bassons, Positif. Paul Kimmage, Rough Ride. Erwann Menthéour, Secret défonce.

- Miyake T, Kung CK, Goldwasser E. Purification of human erythropoietin. J Biol Chem. 1977 Aug 10;252(15):5558-64.

Fluticasone/salmeterol (Advair)

The combination preparation *fluticasone/salmeterol* is a formulation containing fluticasone propionate and salmeterol xinafoate used in the management of asthma and chronic obstructive pulmonary disease (COPD). It is marketed by GlaxoSmithKline under various trade names including *Advair* and *Seretide*.

Formulations

Advair is available in 3 dosage strengths. The smallest dosage is 100/50, the intermediate dosage is 250/50 and the highest dosage is 500/50. The first number in the dosage description is how many micrograms of fluticasone propionate and the second number how many micrograms of salmeterol.

Internationally the fluticasone/salmeterol combination is delivered by a number of devices, including standard aerosol metered dose inhalers (brand name "Evohaler®" in the UK) or dry-powder devices termed "Accuhaler" in the UK and Australia, and "Diskus" in the U.S. These purple disk-shaped containers are about 3.5 inches (8.9 cm) across and about 1 inch thick (2.5 cm). The diskus container holds small pellets of the drug combination, which are crushed on a dose-per-dose basis into a fine powder utilizing an internal mechanism activated by pressing a small lever on the side of the container. The powder is then inhaled directly into the lungs through a mouthpiece. Fluticasone/salmeterol is usually inhaled two times a day.

Fluticasone, a corticosteriod, is the anti-inflammatory component of the combination, while salmeterol treats constriction of the airways. Together, they relieve the symptoms of coughing, wheezing and shortness of breath better than either fluticasone or someterol taken on its own.

Side effects

The common and minor side effects of this combination are those of its individual drugs. For instance, the use of inhaled corticosteroids is associated with oral candidiasis.

Whilst the use of inhaled steroids and long acting beta-adrenoceptor agonist (LABA) are recommended in asthma guidelines for the resulting improved symptom control,[1] concerns have been raised that salmeterol may increase the small risks of asthma deaths and this additional risk is not reduced with the additional use of inhaled steroids.[2] This seems to occur because although LABAs relieve asthma symptoms, they also promote bronchial inflammation and sensitivity without warning.[3]

In a clinical trial, thirteen people died out of a group of 13,176 people taking ADVAIR.

Other side effects include increased blood pressure, change in heart rate, or an irregular heartbeat.

Footnotes

1. ^ British Thoracic Society & Scottish Intercollegiate Guidelines Network (SIGN). British Guideline on the Management of Asthma. Guideline No. 63. Edinburgh:SIGN; 2004.
2. ^ Salpeter S, Buckley N, Ormiston T, Salpeter E (2006). "Meta-analysis: effect of long-acting beta-agonists on severe asthma exacerbations and asthma-related deaths.". Ann Intern Med *144* (12): 904-12. PMID 16754916.

3. ^ Krishna Ramanujan. "Common asthma inhalers cause up to 80 percent of asthma-related deaths, Cornell and Stanford researchers assert", ChronicalOnline - Cornell University.

Vasoconstrictor

A *vasoconstrictor*, also *vasopressor* and simply *pressor*, is any substance or that acts to cause vasoconstriction (narrowing of the lumena of blood vessels) and usually results in an increase of the blood pressure. The opposite process, vasodilation, is the opening of blood vessels.

Many vasoconstrictors act on specific receptors, such as vasopressin receptors or adrenoreceptors. Vasoconstrictors are also used clinically to increase blood pressure or to reduce local blood flow. Exposure to moderately high levels of stress also induces vasoconstriction.

Vasoconstriction also occurs in superficial blood vessels of warm-blooded animals when their ambient environment is cold; this process diverts the flow of heated blood to the center of the animal, preventing the loss of heat.

Examples of vasoconstrictors

- Antihistamines
    - Adrenaline

Asymmetric dimethylarginine
ATP

- Cannabis
    - Catecholamines
- Cocaine
- Decongestants
    - Endothelin

Phenylephrine
Pseudoephedrine
Neuropeptide Y
Norepinephrine
Tetrahydrozoline hydrochloride (in eye drops)
Thromboxane

See also

- Inotrope
- Vasodilation

Abortifacients

An *abortifacient* is a substance that induces abortion.

History

The ancient Greek colony of Cyrene at one time had an economy based almost entirely on the production and export of Silphium, a powerful abortifacient in the parsley family. Silphium figured so prominently in the wealth of Cyrene that the plant appeared on the obverse and reverse of coins minted there. Silphium, which was native only to that part of Libya, was overharvested by the Greeks and was effectively driven to extinction.

As the Catholic Church gained control of European society, women who dispensed abortifacient herbs found themselves classified as witches and were often persecuted. [1]

Present time

Herbal abortifacients

Many herbs sold "over the counter" today, including Wild carrot, Black cohosh, Pennyroyal, Nutmeg, and Mugwort, are themselves abortifacients. Typically the labeling will contraindicate use by pregnant women, but will not contain an explanation for this contraindication. There are naturally occurring abortifacients like green Papaya and Common Rue though there does not seem to be any available data on their efficacy.

King's American Dispensatory of 1898 recommended a mixture of brewer's yeast and pennyroyal tea as "a safe and certain abortive"

Pharmaceutical abortifacients

The methods of operation of prescription drugs used as abortifacients are better understood than those of traditional herbal remedies, but they have been controversial since the 1980s. The most prominent of these is Mifepristone (also known as "RU-486" and marketed under the brand name "Mifeprex"), which is used in conjunction with Misoprostol (an anti-ulcer drug marketed under the name "Cytotec"). Mifepristone has been approved for inducing abortions in many Western countries since the late 1990s, while this use of Misoprostol is off-label.

Misoprostol alone is sometimes used for self-induced abortion in Latin American countries where legal abortion is not available, and by some immigrants from these countries in the United States who cannot afford a legal abortion.

Pre-implantation labeling controversy

There is controversy as to whether a woman is pregnant at the time of fertilization, or at the implantation of the blastocyst in the uterine lining. Some agents have a proposed back-

up effect of preventing implantation and thus destroying the blastocyst, although their primary effect is to prevent fertilization. American federal and British laws mark the beginning of pregnancy at implantation; thus, these agents are labeled as contraceptives, rather than abortifacients. They are generally not effective if taken after implantation.[2] Labeling of these agents as abortifacient is most ardently supported by those opposed to abortion, [3] usually due to their belief that human life begins at fertilization. The following agents may prevent implantation of a blastocyst, although, in most cases, they merely prevent fertilization:[4]

- Hormonal contraceptives
    - Combined estrogen & Progesterone:
        - Combined oral contraceptive pill ("The Pill")*
        - Contraceptive patch
        - Contraceptive vaginal ring
        - Lunelle (monthly injection)
    - Progesterone used alone:
        - Progesterone only pill (POP)*
        - Depo Provera (injection every three months)
        - Implants (such as Norplant or Implanon)
        - IntraUterine System ("IUS")
- Intrauterine device ("IUD")*
- Some herbal contraceptives may work primarily by preventing implantation

(*) These methods may also be used as Emergency contraception. POPs are also packaged for use as emergency contraception under the brand name "Plan B".

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Quinine

Systematic (IUPAC) name

(2-ethenyl-4-azabicyclo[2.2.2]oct-5-yl)- (6-methoxyquinolin-4-yl)-methanol

Identifiers

CAS number 130-95-0

ATC code M09**AA01** P01**BC01**

PubChem 8549

DrugBank APRD00563

Chemical data

Formula $C_{20}H_{24}N_2O_2$

Mol. weight 324.417 g/mol

Physical data

Melt. point 177 °C (351 °F)

Pharmacokinetic data

Bioavailability **76 to 88%**

Protein binding ~70%

Metabolism Hepatic (mostly CYP3A4 and CYP2C19-mediated)

Half life ~18 hours

Excretion Renal (20%)

Therapeutic considerations

Pregnancy cat. X $_{\text{(U.S.)}}$, D $_{\text{(Au)}}$

Routes Oral

Quinine is a natural white crystalline alkaloid having antipyretic, anti-malarial with analgesic and anti-inflammatory properties and a bitter taste. It is a stereoisomer of quinidine.

Quinine was previously superseded by chloroquine, but is now again the drug of choice for treatment of falciparum malaria because of the rise of chloroquine resistance. Quinine is available with a prescription in the U.S.. Quinine is also used to treat nocturnal leg cramps and arthritis and it has also been used (with limited success) to treat people who had been infected by prions. It was once a popular heroin adulterant.

Mechanism of action

The theorized mechanism of action for quinine and related anti-malarial drugs is that these drugs are toxic to the malaria parasite, specifically by interfering with the parasite's ability to break down and digest hemoglobin, thus starving the parasite and/or causing the build-up of toxic levels of partially degraded hemoglobin in the parasite.

Sources of quinine

Quinine was extracted from the bark of the South American cinchona tree, isolated and named in 1820 by French researchers Pierre Joseph Pelletier and Joseph Caventou. The name was derived from the original Quechua (Native American) word for the cinchona tree bark, "Quina" or "Quina-Quina", which roughly means "bark of bark" or "holly bark". Prior to 1820, the bark was first dried, ground to a fine powder, and then mixed into a liquid (commonly wine) before being drunk.

The large scale use of quinine as a prophylactic started around 1850, although it had been used in un-extracted form by Europeans since at least the early 1600s. Quinine was first used to treat malaria in Rome in 1631. During the 1600s, malaria was endemic to the swamps and marshes surrounding the city of Rome. Over time, malaria was responsible for the death of several Popes, many Cardinals, and countless common citizens of Rome. Most of the priests trained in Rome had seen malaria victims, and were familiar with the shivering brought on by the cold phase of the disease. In addition to its anti-malarial properties, quinine is an effective muscle relaxant, long used by the Quechua Indians of Peru to halt shivering brought on by cold temperatures. The Jesuit priest Agostino Salumbrino, an apothecary by training who lived in Lima, observed the Quechua using the quinine-containing bark of the cinchoa tree for that purpose. While its effect in treating malaria (and hence malaria-induced shivering) was entirely unrelated to its effect in controlling shivering from cold, it was still the correct medicine for malaria. At the first opportunity, he sent a small quantity to Rome to test in treating malaria. In the years that followed, cinchona bark became one of the most valuable commodities shipped from Peru to Europe.

Cinchona trees remain the only practical source of quinine. However, under wartime pressure, research towards its artificial production was undertaken. A formal chemical synthesis was accomplished in 1944 by R.B. Woodward and W.E. Doering, American chemists. Since then, several more efficient total syntheses have been achieved (see review article in Angewandte Chemie, Int. Ed., 2005, 44, p. 854 ff), but none of them can compete in economic terms with isolation of the alkaloid from natural sources.

Dosing

Quinine is an extremely basic compound and is therefore always presented as a salt. Various preparations that exist include the hydrochloride, dihydrochloride, sulphate, bisulphate, and gluconate. This makes quinine dosing very complicated, because each of the different salts has a different weight:

- quinine base 100mg, is equivalent to
- quinine bisulphate 169mg, is equivalent to
- quinine dihydrochloride 122 mg, is equivalent to

- quinine hydrochloride 122 mg, is equivalent to
- quinine sulphate 121 mg, is equivalent to
- quinine gluconate 160mg.

All quinine salts may be given orally or intravenously (IV); quinine gluconate may also be given intramuscularly (IM) or rectally (PR). [1][2] The main problem with the rectal route is that the dose can be expelled before it is completely absorbed, but this can be rectified by giving half dose again.

The IV dose of quinine is 8mg/kg of quinine base every eight hours; the IM dose is 12.8mg/kg of quinine base twice daily; the PR dose is 20mg/kg of quinine base twice daily. Treatment should be given for seven days.

The preparations available in the UK are quinine sulphate (200mg or 300mg tablets) and quinine hydrochloride (300mg/ml for injection). Quinine is not licensed for IM or PR use in the UK. The adult dose in the UK is 600mg quinine dihydrochloride IV or 600mg quinine sulphate PO every eight hours.

In the US, quinine sulphate is available as 324mg tablets; the adult dose is two tablets every eight hours. There is no injectable preparation of quinine licensed in the US: quinidine is used instead;[3][4].

Side effects

It is usual for quinine in therapeutic doses to cause cinchonism; in rare cases, it may even cause death (usually by pulmonary edema). The development of mild cinchonism is not a reason for stopping or interrupting quinine therapy and the patient should be reassured. Blood glucose levels and electrolyte concentrations must be monitored when quinine is given by injection; the patient should also ideally be in cardiac monitoring when the first quinine injection is given (these precautions are often unavailable in developing countries where malaria is most a problem).

Cinchonism is much less common when quinine is given by mouth, however, oral quinine is not well tolerated (quinine is exceedingly bitter and many patients will vomit up quinine tablets): other drugs such as Fansidar® (sulfadoxine with pyrimethamine) or Malarone® (proguanil with atovaquone) are often used when oral therapy is required. Blood glucose, electrolyte and cardiac monitoring are not necessary when quinine is given by mouth.

Quinine can cause paralysis if accidentally injected into a nerve.

Quinine is extremely toxic in overdose and the advice of a poisons specialist should be sought immediately.

Quinine and pregnancy

In very large doses, quinine also acts as an abortifacient; in the U.S., quinine is classed as a Category X teratogen by the Food and Drug Administration, meaning that it can cause birth defects (especially deafness) if taken by a woman during pregnancy. In the UK, the recommendation is that pregnancy is not a contra-indication to quinine therapy for falciparum malaria (which directly contradicts the US recommendation), although it should

be used with caution; the reason for this is that the risks to the pregnancy are small and theoretical, as opposed to the very real risk of death from falciparum malaria.

Quinine and interactions with other diseases

Quinine can cause haemolysis in G6PD deficiency, but again, this risk is small and the physician should not hesitate to use quinine in patients with G6PD deficiency when there is no alternative available. Quinine can also cause drug-induced immune thrombocytopenic purpura (ITP), with quinine being the culprit.

Quinine can cause abnormal heart rhythms and should be avoided if possible in patients with atrial fibrillation, conduction defects or heart block.

Quinine must not be used in patients with haemoglobinuria, myasthenia gravis or optic neuritis, because it worsens these conditions.

Non-medical uses of quinine

Quinine is a flavour component of tonic water and bitter lemon. According to tradition, the bitter taste of anti-malarial quinine tonic led British colonials in India to mix it with gin, thus creating the gin and tonic cocktail, which is still popular today in both India and Great Britain, and in other former British colonies.

In the United States, the Food and Drug Administration limits tonic water quinine to 83 ppm, which is one-half to one-quarter the concentration used in therapeutic tonic.

In France, quinine is an ingredient of an apéritif known as Quinquina.

Quinine is often added to street drugs cocaine or ketamine in order to "cut" the product and make more profit.

Because of its relatively constant and well-known fluorescence quantum yield, quinine is also used in photochemistry as a common fluorescence standard.

In Canada, quinine is an ingredient in the carbonated chinotto beverage called Brio.

In the UK, quinine is an ingredient in the carbonated and caffienated beverage, Irn-Bru.

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See also

- Pharmacology

Gin and tonic

A *gin and tonic*, is a cocktail made with gin and tonic water, usually garnished with a slice of lime and served over ice. The ratio of gin to tonic water varies from equal amounts to one part gin for every three parts tonic.

History

This cocktail was introduced by the British in India. Tonic water contains quinine, which was used to prevent malaria. Because the tonic water consumed to prevent malaria in the 19th century was extremely bitter, gin was added to make it more palatable. Although there is less medical use today for the consumption of tonic water, the gin and tonic remains a popular drink. Tonic water available today contains less quinine and is consequently less bitter (usually sweetened). Because of this connection to warmer climates and its refreshing nature, this cocktail is more popular during the warmer months.

Lore has it that the sheer quantity of limes (for the prevention of scurvy) and quinine (for the aforementioned prevention of malaria), was so unpalatable that the only way to get the members of the British Army to consume the prescribed amount was with the addition of gin. [[1]]

In popular culture

The gin and tonic has gained a central place in cultural and literary life, appearing as a bit part in numerous novels. One such example is in the Hitchhiker's Guide to the Galaxy series, where it is stated that eighty-five percent of the races in the galaxy have each independently developed drinks that are pronounced the same, but spelled differently (such as jynnantonnyx), and which bear no resemblance to one another other than the pronunciation of the name. The reason for this is one of the great mysteries of the universe.

The gin and tonic was the usual drink of Bertie Wooster when he was in need of refreshment or, more often, fortification to help face the many problems that cropped up in his life.

It was the preferred drink of Mrs. Slocombe (played by Mollie Sugden) of Are You Being Served?, as she couldn't bear neat gin.

British singer Nik Kershaw's 1983 hit song I Won't Let the Sun Go Down on Me includes the line "Forty winks in the lobby, make mine a g&t."

In Big Bad Voodoo Daddy's song You & Me & The Bottle Makes Three Tonight (Baby) "a gin and tonic sounds mighty mighty good to me."

In the episode of The Simpsons entitled Flaming Moe's, Moe the bartender looks at a chart of cocktail drinks and says, "Gin and... tonic? Do they mix?"

In the Barenaked Ladies song "Alcohol" it is mentioned in the lyric "A malibu and coke for you, a g&t for me."

The Spiritual Beggars song "Angel of Betrayal" includes the lyrics "Gin and Tonic rules/Blood on the floor/Burn marks from cigarettes/My throat pleads for more".

Oasis' 1994 debut single "Supersonic" features the lyric "I'm feelin' Supersonic, give me gin and tonic."

It was the preferred drink of fictional character John Constantine from the comic series Hellblazer.

It is featured in the Ramones song "Somebody put something in my drink" in the line "Tanqueray and tonic/ my favorite drink/ I don't like anything/ colored pink"

It is referenced in Billy Joel's famous song "Piano Man" in the line "There's an old man sitting next to me/ making love to his tonic and gin"

Reverend Horton Heat have a song named "Gin and Tonic Blues" and the lyrics are just: "I need a Gin'n'Tonic water, baby/Gin'n'Tonic water feelin' better/Give me a Gin'n'Tonic/Gin'n'Tonic/I need it now! (repeat many times)"

Pete Doherty and Carl Barat of The Libertines are both very fond of gin. Carl has written a song called 'Gin And Milk' and Pete has written one called 'Gang Of Gin'[citation needed]. Pete sings about "met two fellas over gin and mixers" in the song "La Belle Et La Bête" and "Well, I'll confess all of my sins after several large gins" in "Music When The Lights Go Out".

Adam Sandler references it in "The Chanukah Song" in the line "Drink your gin and tonic-ah and smoke your marijuani-kah"

Similar Drinks

Sometimes gin is mixed with Sprite, 7up or even ginger ale and garnished with lemon or lime. The sweeter soft drinks are sometimes preferred to tonic water. Although none of these are actually a gin & tonic, they are sometimes called so.

Sometimes apple juice or apple schnapps can be added to a gin and tonic. This is referred to as a GTA or Grand Theft Auto.

Tonic water

Tonic water (or *Indian tonic water*) is a carbonated soft drink flavoured with quinine. The drink gains its name from the medicinal effects of this slightly bitter flavouring.

The quinine was added to the drink as a prophylactic against malaria, since it was originally intended for consumption in tropical areas of India and Africa where that disease is endemic.

Tonic water originally contained only carbonated water and quinine, and it contained a large amount of the latter. However, most tonic water today contains a medically insignificant amount of quinine, and is thus used for its flavor only. It is consequently less bitter, and is also usually sweetened. Some manufacturers also produce diet tonic water.

In the United States, the Food and Drug Administration limits tonic water quinine to 83 ppm (83 mg per litre if calculated by mass), which is one-half to one-quarter the concentration used in therapeutic tonic.

Tonic water is often used as a mixer for alcoholic spirits, especially gin (the mixture commonly known as a gin and tonic).

Tonic water with lemon or lime flavor added is known as bitter lemon or bitter lime, respectively. Such soft drinks are more popular in Europe than in the United States.

Tonic water will glow under ultraviolet light, due to the quinine in it.

Brands of tonic water:

- Canada Dry

Cantrell
Cunnington
Seagram's
Schweppes
Royal Club
Nordic Mist by Coca-Cola Company
Kinley by Coca-Cola Company
Krest by Coca-Cola Company
Antarctica by Ambev (Brazil)
Schin Tonica, made by Schincariol (Brazil)
Finches by Gleeson (Ireland)
Paso de los Toros by PepsiCo Inc. (Uruguay)

Analgesics

An *analgesic* (colloquially known as a *painkiller*) is any member of the diverse group of drugs used to relieve pain (achieve analgesia). This derives from Greek an-, "without", and -algia, "pain". Analgesic drugs act in various ways on the peripheral and central nervous system; they include paracetamol (acetaminophen), the nonsteroidal anti-inflammatory drugs (NSAIDs) such as the salicylates, narcotic drugs such as morphine, synthetic drugs with narcotic properties such as tramadol, and various others. Some other classes of drugs not normally considered analgesics are used to treat neuropathic pain syndromes; these include tricyclic antidepressants and anticonvulsants.

The major classes

Paracetamol and NSAIDs

The exact mechanism of action of paracetamol is uncertain, but it appears to be acting centrally. Aspirin and the NSAIDs inhibit cyclooxygenase, leading to a decrease in prostaglandin production; this improves pain and also inflammation (in contrast to paracetamol and the opioids).

Paracetamol has few side effects, but dosing is limited by possible hepatotoxicity (potential for liver damage). NSAIDs may predispose to peptic ulcers, renal failure, allergic reactions, and hearing loss. They may also increase the risk of hemorrhage by affecting platelet function. The use of certain NSAIDs in children under 16 suffering from viral illness may contribute to Reye's syndrome.

COX-2 inhibitors

These drugs have been derived from NSAIDs. The cyclooxygenase enzyme inhibited by NSAIDs was discovered to have at least 2 different versions: COX1 and COX2. Research suggested that most of the adverse effects of NSAIDs were mediated by blocking the COX1 (constitutive) enzyme, with the analgesic effects being mediated by the COX2 (inducible) enzyme. The COX2 inhibitors were thus developed to inhibit only the COX2 enzyme (traditional NSAIDs block both versions in general). These drugs (such as rofecoxib and celecoxib) are equally effective analgesics when compared with NSAIDs, but cause less gastrointestinal hemorrhage in particular. However post-launch data indicated increased risk of cardiac and cerebrovascular events with these drugs, and rofecoxib was subsequently withdrawn from the market. The role for this class of drug is currently hotly debated.

Opiates and morphinomimetics

Morphine, the archetypal opioid, and various other substances (e.g. pethidine, oxycodone, hydrocodone, diamorphine) all exert a similar influence on the cerebral opioid receptor system. Tramadol and buprenorphine are thought to be partial agonists of the

opioid receptors. Dosing of all opioids may be limited by opioid toxicity (confusion, myoclonic jerks and pinpoint pupils), but there is no dose ceiling in patients who tolerate this.

Opioids, while very effective analgesics, may have some unpleasant side-effects. Up to 1 in 3 patients starting morphine may experience nausea and vomiting (generally relieved by a short course of antiemetics). Pruritus (itching) may require switching to a different opioid. Constipation occurs in almost all patients on opioids, and laxatives (lactulose, macrogol-containing or co-danthramer) are typically co-prescribed.

When used appropriately, opioids and similar narcotic analgesics are safe and effective, carrying relatively little risk of addiction. Occasionally, gradual tapering of the dose is required to avoid withdrawal symptoms.

Specific agents

In patients with chronic or neuropathic pain, various other substances may have analgesic properties. Tricyclic antidepressants, especially amitriptyline, have been shown to improve pain in what appears to be a central manner. The exact mechanism of carbamazepine, gabapentin and pregabalin is similarly unclear, but these anticonvulsants are used to treat neuropathic pain with modest success.

Specific forms and uses

Combinations

Analgesics are frequently used in combination, such as the paracetamol and codeine preparations found in many non-prescription pain relievers. They can also be found in combination with vasoconstrictor drugs such as pseudoephedrine for sinus-related preparations, or with antihistamine drugs for allergy sufferers.

The use of paracetamol concurrently with opiates has been shown to have beneficial synergistic effects and it is generally recommended that they are prescribed together.

Topical or systemic

Topical analgesia is generally recommended to avoid systemic side-effects. Painful joints, for example, may be treated with an ibuprofen- or diclofenac-containing gel; capsaicin also is used topically. Lidocaine and steroids may be injected into painful joints for longer-term pain relief. Lidocaine is also used for painful mouth sores and to numb areas for dental work and minor medical procedures.

Psychotropic agents

Tetrahydrocannabinol and some other cannabinoids, either from the Cannabis sativa plant or synthetic, have analgesic properties, although the use of cannabis derivatives is illegal in many countries. Other psychotropic analgesic agents include ketamine (an NMDA

receptor antagonist), clonidine and other ±2-adrenoreceptor agonists, and mexiletine and other local anaesthetic analogues.

Addiction

In the United States in recent years, however, there has been a wave of new addictions to prescription narcotics such as oxycodone (OxyContin) and hydrocodone (Vicodin, Lortab etc.) when available in pure formulations as opposed to combined with other medications (as in Percocet which contains both oxycodone and acetaminophen/paracetamol).

References

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- Bandolier pain site (Oxford pain group)

Non-steroidal anti-inflammatory drugs

Non-steroidal anti-inflammatory drugs, usually abbreviated to *NSAID*s, are drugs with analgesic, antipyretic and anti-inflammatory effects - they reduce pain, fever and inflammation. The term "non-steroidal" is used to distinguish these drugs from steroids, which (amongst a broad range of other effects) have a similar eicosanoid-depressing, anti-inflammatory action. NSAIDS are unusual in that they are non-narcotic. NSAIDs are sometimes also referred to as *non-steroidal anti-inflammatory agents/analgesics* (*NSAIAs*). The most prominent members of this group of drugs are aspirin and ibuprofen. Paracetamol (acetaminophen) has negligible anti-inflammatory activity, and is strictly speaking not an NSAID.

Beginning in 1829, with the isolation of salicylic acid from the folk remedy willow bark, NSAIDs have become an important part of the pharmaceutical treatment of pain (at low doses) and inflammation (at higher doses). Part of the popularity of NSAIDs is that, unlike opioids, they do not produce sedation or respiratory depression and have a very low addiction rate. NSAIDs, however, are not without their own problems (see below). Certain NSAIDs, including ibuprofen and aspirin, have become accepted as relatively safe and are available over-the-counter without prescription.

Mode of action

Most NSAIDs act as non-selective inhibitors of the enzyme cyclooxygenase, inhibiting both the cyclooxygenase-1 (COX-1) and cyclooxygenase-2 (COX-2) isoenzymes. Cyclooxygenase catalyses the formation of prostaglandins and thromboxane from arachidonic acid (itself derived from the cellular phospholipid bilayer by phospholipase A2). Prostaglandins act (among other things) as messenger molecules in the process of

inflammation. This mechanism of action was elucidated by John Vane, who later received a Nobel Prize for his work.

Examples

NSAIDs can be broadly classified based on their chemical structure. NSAIDs within a group will tend to have similar characteristics and tolerability. There is little difference in clinical efficacy between the NSAIDs when used at equivalent doses. Rather, differences between compounds tended to be with regards to dosing regimens (related to the compound's elimination half-life), route of administration, and tolerability profile. Some more common examples are given below.

Paracetamol (acetaminophen), owing to its inhibitory action on cyclooxygenase, is sometimes grouped together with the NSAIDs. Paracetamol, however, does not have any significant anti-inflammatory properties and is not a true NSAID. Though it has not been clearly elucidated, it is suspected that this lack of anti-inflammatory action may be due to the paracetamol inhibiting cyclooxygenase predominantly in the central nervous system. There is also some speculation that paracetamol acts through the inhibition of the recently discovered COX-3 isoform (see below).

Salicylates

- Aspirin
  - Amoxiprin
  Benorilate
  Choline magnesium salicylate
  Diflunisal
  Faislamine
  Methyl salicylate
  Salicyl salicylate (salsalate)

Arylalkanoic acids

- Diclofenac
  - Aceclofenac
  Acemetacin
  Bromfenac
  Etodolac
- Indometacin
  - Ketorolac
  Nabumetone

Sulindac
Tolmetin

2-Arylpropionic acids (profens)

- Ibuprofen
    - Carprofen
    - Fenbufen
  Fenoprofen
  Flurbiprofen
- Ketoprofen
    - Loxoprofen
- Naproxen
    - Tiaprofenic acid

N-Arylanthranilic acids (fenamic acids)

- Mefenamic acid
- Meclofenamic acid
  Tolfenamic acid

Pyrazolidine derivatives

- Phenylbutazone
- Azapropazone
  Metamizole
  Oxyphenbutazone

Oxicams

- Piroxicam
    - Lornoxicam
  Meloxicam
  Tenoxicam

Coxibs

- Celecoxib
- Etoricoxib
  Lumiracoxib
  Parecoxib

- Rofecoxib (withdrawn from market)
- Valdecoxib (withdrawn from market)

Sulphonanilides

- Nimesulide

Others

- Licofelone
Omega-3 Fatty Acids

Uses

NSAIDs are usually indicated for the treatment of acute or chronic conditions where pain and inflammation are present. Research continues into their potential for prevention of colorectal cancer, and treatment of other conditions, such as cancer and cardiovascular disease.

NSAIDs are generally indicated for the symptomatic relief of the following conditions: (Rossi, 2006)

- Rheumatoid arthritis
Osteoarthritis
Inflammatory arthropathies (e.g. ankylosing spondylitis, psoriatic arthritis, Reiter's syndrome)
Acute gout
Dysmenorrhoea
Metastatic bone pain
Headache and migraine
Postoperative pain
Mild-to-moderate pain due to inflammation and tissue injury
Pyrexia
Renal colic

Aspirin, the only NSAID able to irreversibly inhibit COX-1, is also indicated for inhibition of platelet aggregation; an indication useful in the management of arterial thrombosis and prevention of adverse cardiovascular events.

In 2001, NSAIDs accounted for 70,000,000 prescriptions and 30 billion over-the-counter doses sold annually in the United States. (Green, 2001). With the aging of the Baby Boomer generation and the associated rise in the incidence of osteoarthritis and other such conditions for which NSAIDs are indicated, the use of NSAIDs may increase further still.

Pharmacokinetics

Most NSAIDs are weak acids, with a pKa of 3-5. They are absorbed well from the stomach and intestinal mucosa. They are highly protein-bound in plasma (typically >95%), usually to albumin, so that their volume of distribution typically approximates to plasma volume. Most NSAIDs are metabolised in the liver by oxidation and conjugation to inactive metabolites which are typically excreted in the urine, although some drugs are partially excreted in bile.

Metabolism may be abnormal in certain disease states, and accumulation may occur even with normal dosage.

Ibuprofen and diclofenac have short half-lives (2-3 hours). Some NSAIDs (typically oxicams) have very long half-lives (e.g. 20-60 hours).

Adverse effects

The widespread use of NSAIDs has meant that the adverse effects of these relatively safe drugs have become increasingly prevalent. The two main adverse drug reactions (ADRs), associated with NSAIDs relate to gastrointestinal (GI) effects and renal effects of the agents.

These effects are dose-dependent, and in many cases severe enough to pose the risk of ulcer perforation, upper gastrointestinal bleeding, and death, limiting the use of NSAID therapy. An estimated 10-20% of NSAID patients experience dyspe gastrointestinal (GI) effects and renal epsia, and NSAID-associated upper gastrointestinal adverse events are estimated to result in 103,000 hospitalizations and 16,500 deaths per year in the United States, and represent 43% of drug-related emergency visits. Many of these events are avoidable; a review of physician visits and prescriptions estimated that unnecessary prescriptions for NSAIDs were written in 42% of visits. (Green, 2001)

Cardiovascular risk

A recent meta-analysis of all trials comparing non-steroidal anti-inflammatory drugs found a 80% increase in the risk of myocardial infarction with both newer Cox-2 antagonists and high dose traditional anti-inflammatories compared with placebo, with the important exception of naproxen, which was not associated with an increased cardiovascular risk (Kearney et al, BMJ 2006;332:1302-1308).

Gastrointestinal ADRs

The main ADRs associated with use of NSAIDs relate to direct and indirect irritation of the gastrointestinal tract (GIT). NSAIDs cause a dual insult on the GIT - the acidic molecules directly irritate the gastric mucosa; and inhibition of COX-1 reduces the levels of protective prostaglandins.

Common gastrointestinal ADRs include: (Rossi, 2006)

- Nausea
- Dyspepsia
- Gastric ulceration/bleeding
- Diarrhea

Risk of ulceration increases with duration of therapy, and with higher doses. In attempting to minimise GI ADRs, it is prudent to use the lowest effective dose for the shortest period of time, a practice which studies show is not often followed.

There are also some differences in the propensity of individual agents to cause gastrointestinal ADRs. Indomethacin, ketoprofen and piroxicam appear to have the highest

prevalence of gastric ADRs, while ibuprofen (lower doses) and diclofenac appear to have lower rates. (Rossi, 2006)

Certain NSAIDs, such as aspirin, have been marketed in enteric-coated formulations which are claimed to reduce the incidence of gastrointestinal ADRs. Similarly, there is a belief that rectal formulations may reduce gastrointestinal ADRs. However, in consideration of the mechanism of such ADRs and indeed in clinical practice, these formulations have not been shown to have a reduced risk of GI ulceration. (Rossi, 2006)

Commonly, gastrointestinal adverse effects can be reduced through suppressing acid production, by concomitant use of a proton pump inhibitor, e.g. omeprazole; or the prostaglandin analogue misoprostol. Misoprostol is itself associated with a high incidence of gastrointestinal ADRs (diarrhoea). While these techniques may be effective, they prove to be expensive for maintenance therapy.

Renal ADRs

NSAIDs are also associated with a relatively high incidence of renal ADRs. The mechanism of these renal ADRs is probably due to changes in renal haemodynamics (bloodflow), ordinarily mediated by prostaglandins, which are affected by NSAIDs. Horses are particularly prone to these adverse affects compared to other domestic animal species.

Common ADRs associated with altered renal function include: (Rossi, 2006)

- Salt and fluid retention
- Hypertension

These agents may also cause renal impairment, especially in combination with other nephrotoxic agents. Renal failure is especially a risk if the patient is also concomitantly taking an ACE inhibitor and a diuretic - the so-called "triple whammy" effect. (Thomas, 2000)

In rarer instances NSAIDs may also cause more severe renal conditions: (Rossi, 2006)

- Interstitial nephritis

Nephrotic syndrome
Acute renal failure
Acute tubular necrosis

Photosensitivity

Photosensitivity is a commonly overlooked adverse effect of many of the NSAIDs. (Moore, 2002) It is somewhat ironic that these anti-inflammatory agents may themselves produce inflammation in combination with exposure to sunlight. The 2-arylpropionic acids have proven to be the most likely to produce photosensitivity reactions, but other NSAIDs have also been implicated including piroxicam, diclofenac and benzydamine.

Benoxaprofen, since withdrawn due to its hepatotoxicity, was the most photoactive NSAID observed. The mechanism of photosensitivity, responsible for the high photoactivity of the 2-arylpropionic acids, is the ready decarboxylation of the carboxylic acid moiety. The specific absorbance characteristics of the different chromophoric 2-aryl substituents, affects the decarboxylation mechanism. While ibuprofen is somewhat of an exception, having weak absorption, it has been reported to be a weak photosensitising agent.

During pregnancy

NSAIDs are not recommended during pregnancy, particularly during the third trimester. While NSAIDs as a class are not direct teratogens, they may cause premature closure of the fetal ductus arteriosus and renal ADRs in the fetus. Additionally, they are linked with premature birth (Ostensen & Skomsvoll, 2004). Aspirin, however, is used together with heparin in pregnant women with antiphospholipid antibodies (Cervera & Balasch, 2004).

In contrast, paracetamol (acetaminophen) is regarded as being safe and well-tolerated during pregnancy (Graham et al., 2005). Doses should be taken as prescribed, due to risk of hepatotoxicity with overdoses (Wilkes et al, 2005).

Other ADRs

Common ADRs, other than listed above, include: raised liver enzymes, headache, dizziness (Rossi, 2006).

Uncommon ADRs include: heart failure, hyperkalaemia, confusion, bronchospasm, rash (Rossi, 2006). Ibuprofen may also rarely cause irritable bowel syndrome symptoms.

Most NSAIDs penetrate poorly into the central nervous system (CNS). However, the COX enzymes are expressed constitutively in some areas of the CNS, meaning that even limited penetration may cause adverse effects such as somnolence and dizziness.

Chirality

Most NSAIDs are chiral molecules (diclofenac is a notable exception). However, the majority are prepared in a racemic mixture. Typically, only a single enantiomer is pharmacologically active. For some drugs, (typically profens) an isomerase enzyme exists in vivo which converts the inactive enantiomer into the active form, although its activity varies widely in individuals. This phenomenon is likely to be responsible for the poor correlation between NSAID efficacy and plasma concentration observed in older studies, when specific analysis of the active enantiomer was not performed.

Ibuprofen and ketoprofen are now available in single, active enantiomer preparations (*dexibuprofen* and *dexketoprofen*), which purport to offer quicker onset and an improved side-effect profile. Naproxen has always been marketed as the single active enantiomer.

Newer NSAIDs: selective COX inhibitors

COX-2 inhibitors

The discovery of COX-2 in 1991 by Daniel L. Simmons at Brigham Young University raised the hope of developing an effective NSAID without the gastric problems characteristic of these agents. It was thought that selective inhibition of COX-2 would result in anti-inflammatory action without disrupting gastroprotective prostaglandins.

COX-1 is a constitutively expressed enzyme with a "house-keeping" role in regulating many normal physiological processes. One of these is in the stomach lining, where

prostaglandins serve a protective role, preventing the stomach mucosa from being eroded by its own acid. When non-selective COX-1/COX-2 inhibitors (such as aspirin, ibuprofen, and naproxen) lower stomach prostaglandin levels, these protective effects are lost and ulcers of the stomach or duodenum and potentially internal bleeding can result. COX-2 is an enzyme facultatively expressed in inflammation, and it is inhibition of COX-2 that produces the desirable effects of NSAIDs.

The relatively selective COX-2 inhibiting oxicam, meloxicam, was the first step towards developing a true COX-2 selective inhibitor. Coxibs, the newest class of NSAIDs, can be considered as true COX-2 selective inhibitors, and include celecoxib, rofecoxib, valdecoxib, parecoxib and etoricoxib.

Controversies with COX-2 inhibitors

While it was hoped that this COX-2 selectivity would reduce gastrointestinal adverse drug reactions (ADRs), there is little conclusive evidence that this is true. The original study touted by Searle (now part of Pfizer), showing a reduced rate of ADRs for celecoxib, was later revealed to be based on preliminary data - the final data showed no significant difference in ADRs when compared with diclofenac.

Rofecoxib however, which has since been withdrawn, had been shown to produce significantly fewer gastrointestinal ADRs compared to naproxen. (Bombardier et al, 2000). This study, the VIGOR trial, raised the issue of the cardiovascular safety of the coxibs - a statistically insignificant increase in the incidence of myocardial infarctions was observed in patients on rofecoxib. Further data, from the APPROVe trial, showed a relative risk of cardiovascular events of 1.97 versus placebo - a result which resulted in the worldwide withdrawal of rofecoxib in October 2004.

COX-3 inhibitors

Simmons also co-discovered COX-3 in 2002 and analyzed this new isozyme's relation to paracetamol (acetaminophen), arguably the most widely used analgesic drug in the world. (Chandrasekharan et al, 2002). The authors postulated that inhibition of COX-3 could represent a primary central mechanism by which these drugs decrease pain and possibly fever.

The clinical ramifications and knowledge of COX isozymes are rapidly expanding and may offer significant hope for future treatments of pain, inflammation, and fever.

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External links

- US National Library of Medicine: MedlinePlus® Drug Information: Anti-inflammatory Drugs, Nonsteroidal (Systemic)

NSAID nephropathy

- NSAID or Non-steroidal anti-inflammatory drug, are drugs with analgesic, antipyretic and anti-inflammatory effects - they reduce pain, fever and inflammation. The term "non-steroidal" is used to distinguish these drugs from steroids which have simmiliar effects.
- Nephropathy or nephrosis refers to damage to or disease of the kidney. Therefore *NSAID Nephropathy* is damage to the kidney as a result of taking NSAID drugs.

Symptoms

- Acute renal failure secondary to renal hemodynamic changes Interstitial nephritis with or without proteinuria/nephrotic syndrome Hypertension

Epidemiology

Epidemiology is the scientific study of factors affecting the health and illness of individuals and populations

- Very low, 1% to 3% of patient exposed experience one of the previously mentioned
- Delayed onset from initial use of NSAID
- Described with use in all types of NSAIDs

The number of people taking NSAIDs is very high, offsetting low rate per user to high rate per population.

Pathophysiology

Pathophysiology is the study of the disturbance of normal mechanical, physical, and biochemical functions that a disease causes, or that which causes the disease

Inhibition of renal prostaglandin synthesis interferes with renal hemodynamics.

PGI2, PGE2 are responsible for:

- vasodilation in the arterioles and glomeruli decreased Na transport and natriuresis in the distal tubules Interferes with ADH action in the distal tubules

TXA2 shown to vasoconstrict glomeruli

Clinical features: NSAID-Induced hemodynamic deterioration of Renal Function

- Prostoglandin Inhibtion leads to further renal vasoconstriction
Especially in setting of already vasocontricted states such as CHF, nephrotic syndrome, cirrhosis, volume depletion, CRI
30% of patient with CRI on NSAIDS develop this syndrome
Elderly also at increased risk mostly secondary to pharmacokinetics
Fully reversible if caught early
Rarely the sole cause of ESRD

Clinical Features: NSAID Associated Tubulointerstial nephritis

- Heavy Proteinuria/Nephrotic syndrome – 83%
Eosinophilia and Eosinophiluria uncommon – 19%
Focal tubulointerstitial infiltrates on biopsy
Some + immunofluorescence for IgG, IgA, IgM and C3 in interstitial membranes
Non-oliguric course typical
Variable delayed onset
May take weeks to many months to resolve, after stopping NSAID

Clinical Features: NSAID associated Hypertension

- Usually only a modest increase in BP – an average increase of 6-8mmHg pf MAP in patient on NSAIDs
- NSAIDs mitigate effects of B-blockers and diuretics
- CCB less susceptible to effects of NSAIDs
- Elderly, Blacks, low renin hypertension most susceptible

Clinical Oddballs

- Minimal change disease/Nephrotic syndrome
- Hyperkalemia – NSAIDs anecdotally used to treat Barter's

Treatment

- Withdraw NSAIDs
- Avoid Nephrotoxic meds
- +/- Steroids with NSAID associated tubulointerstitial nephritis

See also

- NSAID

Aspirin

Systematic (IUPAC) name 2-(acetyloxy)benzoic acid

Identifiers
CAS number 50-78-2

ATC code **A01**AD05 **B01**AC06**, N02**BA01

PubChem 2244

DrugBank APRD00264

Chemical data

Formula C***9***H***8***O***4*** C6H4(OCOCH3)COOH

Mol. weight 180.16 g/mol

Synonyms 2-acetyloxybenzoic acid, 2-acetoxybenzoic acid, acetylsalicylate, acetylsalicylic acid, O-acetylsalicylic acid

Physical data

Density 1.40 g/cm^3

Melt. point 138-140 °C (-82 °F)

Boiling point 140 °C (284 °F)

Solubility in water 4.6 mg/mL (20 °C)

Pharmacokinetic data

Bioavailability rapid & complete

Protein binding 99.6%

Metabolism hepatic

Half life 300-650mg dose 3.1-3.2hrs, 1 g dose 5 hours, 2 g dose 9 hours

Excretion renal

Therapeutic considerations

Pregnancy cat. C(AU) C(US)

Legal status GSL(UK) OTC(US)

Routes oral

Aspirin or *acetylsalicylic acid* (acetosal) is a drug in the family of salicylates, often used as an analgesic (against minor pains and aches), antipyretic (against fever), and anti-inflammatory. It has also an antiplatelet ("blood-thinning") effect and is used in long-term low-doses to prevent heart attacks and cancer.

Low-dose long-term aspirin irreversibly blocks the formation of thromboxane A2 in platelets, producing an inhibitory effect on platelet aggregation, and this blood-thinning property makes it useful for reducing the incidence of heart attacks. Aspirin produced for this purpose often comes in 75 or 81 mg dispersible tablets and is sometimes called "Junior aspirin" or "Baby aspirin." High doses of aspirin are also given immediately after an acute heart attack. These doses may also inhibit the synthesis of prothrombin and may therefore produce a second and different anticoagulant effect.

Several hundred fatal overdoses of aspirin occur annually, but the vast majority of its uses are beneficial. Its primary undesirable side effects, especially in higher doses, are gastrointestinal distress (including ulcers and stomach bleeding) and tinnitus. Another side effect, due to its anticoagulant properties, is increased bleeding in menstruating women.

Because there appears to be a connection between aspirin and Reye's syndrome, aspirin is no longer used to control flu-like symptoms or the symptoms of chickenpox in minors.[1]

Aspirin was the first discovered member of the class of drugs known as non-steroidal anti-inflammatory drugs (NSAIDs), not all of which are salicylates, though they all have similar effects and a similar action mechanism.

Aspirin as genericized trademark

The brand name Aspirin was coined by the Bayer company of Germany. In some countries the name is used as a generic term for the drug rather than the manufacturer's trademark. In countries in which Aspirin remains a trademark, the initialism *ASA* (for acetylsalicylic acid) is used as a generic term (*ASS* in German-language countries, for Acetylsalicylsäure; *AAS* in Spanish- and Portuguese-language countries, for ácido acetilsalicílico and in French-language countries, for acide acétylsalicylique).

The name "aspirin" is composed of a- (from the acetyl group) -spir- (from the plant genus Spiraea) and -in (a common ending for drugs at the time). It has also been stated that the name originated by another means. "As" referring to AcetylSalicylic and "pir" in reference to one of the scientists who was able to isolate it in crystalline form, Raffaele Piria. Finally "in" due to the same reasons as stated above.

On March 6, 1899 Bayer registered it as a trademark. However, the German company lost the right to use the trademark in many countries as the Allies seized and resold its foreign assets after World War I. The right to use "Aspirin" in the United States (along with all other Bayer trademarks) was purchased from the U.S. government by Sterling Drug in 1918. Even before the patent for the drug expired in 1917, Bayer had been unable to stop competitors from copying the formula and using the name elsewhere, and so, with a flooded market, the public was unable to recognize "Aspirin" as coming from only one manufacturer. Sterling was subsequently unable to prevent "Aspirin" from being ruled a genericized trademark in a U.S. federal court in 1921. Sterling was ultimately acquired by Bayer in 1994, but this did not restore the U.S. trademark. Other countries (such as Canada and many countries in Europe) still consider "Aspirin" a protected trademark.

Discovery

Hippocrates, a Greek physician, wrote in the 5th century BC about a bitter powder extracted from willow bark that could ease aches and pains and reduce fevers. This remedy is also mentioned in texts from ancient Sumer, Lebanon and Assyria. Native Americans have used the bark and the leaves of the willow for medicinal purpose for centuries. The medicinal part of the plant is the inner bark and was used as a pain reliever for a variety of ailments. Cherokees used an infusion of the bark for fever, rheumatic pains, insomnia, dysentery, and sore throats. The Reverend Edward Stone, a vicar from Chipping Norton, Oxfordshire England, noted in 1763 that the bark of the willow was effective in reducing a fever.[2]

The active extract of the bark, called salicin, after the Latin name for the White willow (Salix alba), was isolated to its crystalline form in 1828 by Henri Leroux, a French

pharmacist, and Raffaele Piria, an Italian chemist. Piria was able to convert the substance into a sugar and a second component, which on oxidation becomes salicylic acid.

Salicylic acid was also isolated from meadowsweet (Filipendula ulmaria, formerly classified as Spiraea ulmaria) by German researchers in 1839. While their extract was somewhat effective, it also caused digestive problems such as gastric irritation and bleeding, and diarrhea, and even death when consumed in high doses. In 1853, a French chemist named Charles Frederic Gerhardt neutralized salicylic acid by buffering it with sodium (sodium salicylate) and acetyl chloride, creating acetosalicylic anhydride. Gerhardt's product worked, but he had no desire to market it and abandoned his discovery. In 1897, researcher Arthur Eichengrun and Felix Hoffmann, a research assistant at Friedrich Bayer & Co. in Germany, derivatized one of the hydroxyl functional groups in salicylic acid with an acetyl group (forming acetylsalicylic acid, an acetyl ester). This thereby greatly reduced the negative effects caused by the free phenolic group of salicylic acid. When in the body, the ester (aspirin) is hydrolyzed to free the active drug. This was the first synthetic drug, not a copy of something that existed in nature, and the start of the pharmaceuticals industry.

Hoffmann made some of the formula and gave it to his father, who was suffering from the pain of arthritis and could not stand the side effects of salicylic acid. With good results, he then convinced Bayer to market the new wonder drug. 'Aspirin' was patented on March 6, 1899. It was marketed alongside another of Hoffmann's products, an acetylated synthetic of morphine called 'Heroin' that he invented 11 days after Aspirin. Heroin was initially the more successful of the two painkillers and it was common belief that it was healthier than Aspirin. But, as Heroin's shortcoming of addictiveness became more obvious, Aspirin stepped to the forefront. Aspirin was originally sold as a powder (still the preferred form in many European countries) and was an instant success; in 1915, Bayer introduced Aspirin tablets.

Several claims to invention of acetylsalicylic acid have arisen. Acetylsalicylic acid was already being manufactured by the Chemische Fabrik von Heyden Company in 1897, although without a brand name. Arthur Eichengrün claimed in 1949 that he planned and directed the synthesis of aspirin while Hoffmann's role was restricted to the initial lab synthesis using Eichengrün's process. In 1999, Walter Sneader of the Department of Pharmaceutical Sciences at the University of Strathclyde in Glasgow reexamined the case and agreed with Eichengrün's account. Bayer continues to recognize Felix Hoffmann as aspirin's official inventor. Despite its argued origin, Bayer's marketing was responsible for bringing it to the world.

It was not until the 1970s that the mechanism of action of aspirin and similar drugs called NSAIDs was elucidated (see below).

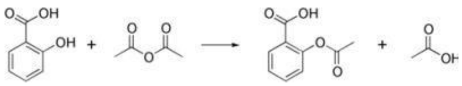
Synthesis of aspirin

Aspirin is commercially synthesized using a two-step process. First, phenol (generally extracted from coal tar) is treated with a sodium base generating sodium phenoxide, which is then reacted with carbon dioxide under high temperature and pressure to yield salicylate, which is acidified, yielding salicylic acid. This process is known as the Kolbe-Schmitt reaction.

Salicylic acid is then acetylated using acetic anhydride, yielding aspirin and acetic acid as a byproduct. It is a common experiment performed in organic chemistry labs, and generally

tends to produce low yields due to the relative difficulty of its extraction from an aqueous state. The trick to getting the reaction to work is to acidify with phosphoric acid and heat the reagents under reflux with a boiling water bath for between 40 to 60 minutes.

The original synthesis of aspirin from salicylic acid involved acetylation with acetyl chloride. Unfortunately, the byproduct from this is hydrochloric acid, which is corrosive and environmentally hazardous. As describe above, it was then later found that acetic anhydride was a better acylating agent, with the byproduct acetic acid formed, which does not have the unwanted properties of hydrochloric acid and can also be recycled.



Formulations containing high concentrations of aspirin often smell of vinegar. This is because aspirin can undergo autocatalytic degradation to salicylic acid in moist conditions, yielding salicylic acid and acetic acid.

Mechanism of action

In 1971, the British pharmacologist, John Robert Vane, who was then employed by the Royal College of Surgeons in London, showed that aspirin had suppressed the production of prostaglandins and thromboxanes. For this piece of research he was awarded both a Nobel Prize in Physiology or Medicine in 1982 and a knighthood.

Aspirin's ability to suppress the production of prostaglandins and thromboxanes is due to its non-competitive (irreversible) inhibition of the cyclooxygenase (COX) enzyme. Cyclooxygenase is required for prostaglandin and thromboxane synthesis. Aspirin acts as an acetylating agent where an acetyl group is covalently attached to a serine residue in the active site of the COX enzyme. This makes aspirin different from other NSAIDS (such as diclofenac and ibuprofen), which are reversible inhibitors.

Prostaglandins are local hormones (paracrine) produced in the body and have diverse effects in the body, including but not limited to transmission of pain information to the brain, modulation of the hypothalamic thermostat, and inflammation. Thromboxanes are responsible for the aggregation of platelets that form blood clots. Heart attacks are primarily caused by blood clots, and their reduction with the introduction of small amounts of aspirin has been seen to be an effective medical intervention. The side-effect of this is that the ability of the blood in general to clot is reduced, and excessive bleeding may result from the use of aspirin.

More recent work has shown that there are at least two different types of cyclooxygenase: COX-1 and COX-2. Aspirin inhibits both of them. Newer NSAID drugs called COX-2 selective inhibitors have been developed that inhibit only COX-2, with the hope for reduction of gastrointestinal side-effects.

However, several of the new COX-2 selective inhibitors have been recently withdrawn, after evidence emerged that COX-2 inhibitors increase the risk of heart attack. It is proposed that endothelial cells lining the arteries in the body express COX-2, and, by selectively inhibiting COX-2, prostaglandins (specifically PGF2) are downregulated with respect to thromboxane levels, as COX-1 in platelets is unaffected. Thus, the protective anti-coagulative

effect of PGF2 is decreased, increasing the risk of thrombus and associated heart attacks and other circulatory problems. Since platelets have no DNA, they are unable to synthesize new COX once aspirin has irreversibly inhibited the enzyme, rendering them "useless": an important difference with reversible inhibitors.

Furthermore, aspirin has 2 additional modes of actions, contributing to its strong analgesic, antipyretic and anti-inflammatory properties:

- It uncouples oxidative phosphorylation in cartilaginous (and hepatic) mitochondria.
- It induces the formation of NO-radicals in the body that enable the white blood cells (leukocytes) to fight infections more effectively. This has been found recently by Dr. Derek W. Gilroy, winning Bayer's International Aspirin Award 2005.

More recent data suggest that salicylic acid and its derivatives will modulate NFkB signaling. NFkB is a transcription factor complex that plays a central role in many biological processes, including inflammation.

Indications

Aspirin, as with many older drugs, has proven to be useful in many conditions. Despite its well-known toxicity it is widely used, since physicians are familiar with its properties. Indications for its use include:

- Fever

Pain (especially useful for some forms of arthritis, osteoid osteoma, and chronic pain)
Migraine
Rheumatic fever (drug of choice)
Kawasaki's disease (along with IVIG)
Pericarditis

- Coronary artery disease
  - Acute myocardial infarction[3]

In addition, aspirin is recommended (low dose, 75-81 mg daily) for the prevention of:

- Myocardial infarction - in patients with either documented coronary artery disease or at elevated risk of cardiovascular disease

Stroke - as secondary prevention (i.e. to prevent recurrence)

In the UK, aspirin can be obtained without a prescription.

Dosage

For adults doses of 300 to 1000 mg are generally taken four times a day for fever or arthritis, with a maximum dose of 8000 mg a day.[4] The correct dose of aspirin depends on the disease process that is being treated. For instance, for the treatment of rheumatic fever, doses near the maximal daily dose have been used historically. For the prevention of myocardial infarction in someone with documented or suspected coronary artery disease, doses as low as 75 mg daily (or possibly even lower) are sufficient.

For those under 12 years of age, the dose previously varied with the age, but aspirin is no longer routinely used in children due to the association with Reye's syndrome; paracetamol or other NSAIDs, such as Ibuprofen, now being used instead. Kawasaki disease remains one of the few indications for aspirin use in children with aspirin initially started at 7.5-12.5 mg/kg body weight taken four times a day for up to two weeks and then continued at 5 mg/kg once daily for a further six to eight weeks.[5]

Toxicity of low-dose aspirin

A recent review states: "....low-dose aspirin increases the risk of major bleeding 2-fold compared with placebo. However, the annual incidence of major bleeding due to low-dose aspirin is modest—only 1.3 patients per thousand higher than what is observed with placebo treatment. Treatment of approximately 800 patients with low-dose aspirin annually for cardiovascular prophylaxis will result in only 1 additional major bleeding episode." Further, "...the cost to prevent one major GI bleeding episode from aspirin in 1 year by substituting clopidogrel therapy would be $1,216,180..."[6]

Contraindications and warnings

- Aspirin should be avoided by those known to be allergic to aspirin, ibuprofen or naproxen.
- Caution should be exercised in those with asthma or NSAID-precipitated bronchospasm.
- It is generally recommended that one seek medical help if symptoms do not improve after a few days of therapy.
- Caution should be taken in patients with kidney disease, peptic ulcers, mild diabetes, gout or gastritis; manufacturers recommend talking to one's doctor before using this medicine.
- Taking aspirin with alcohol increases the chance of gastrointestinal hemorrhage (stomach bleeding).
- Children, including teenagers, are discouraged from using aspirin in cold or flu symptoms as this has been linked with Reye's syndrome.[1]
- Patients with hemophilia or other bleeding tendencies should not take salicylates.
- Some sources recommend that patients with hyperthyroidism avoid aspirin because it elevates T4 levels.
- Pets - aspirin may be used in cats, but only under a veterinarian's strict supervision, as aspirin has a biological half-life of 3 days in cats (cats have trouble breaking down aspirin). Dogs may also use aspirin under a vet's strict supervision, though dogs are more susceptible to aspirin-caused GI bleeds than humans. Aspirin is generally not recommended for pets, though, as there are much safer alternatives for pain relief, and aspirin interacts with several other drugs including cortisones, digoxin, some antibiotics, phenobarbital and furosemide (Lasix)

Common side-effects

- Gastrointestinal complaints (stomach upset, dyspepsia, heartburn, small blood loss). To help avoid these problems, it is recommended that aspirin be taken at or after meals. Undetected blood loss may lead to hypochromic anemia.
- Severe gastrointestinal complaints (gross bleeding and/or ulceration), requiring discontinuation and immediate treatment. Patients receiving high doses and/or long-term treatment should receive gastric protection with high-dosed antacids, ranitidine or omeprazole.
- Frequently, central effects (dizziness, tinnitus, hearing loss, vertigo, centrally mediated vision disturbances, and headaches). The higher the daily dose is, the more likely it is that central nervous system side effects will occur.
- Sweating, seen with high doses, independent from antipyretic action
- Long-term treatment with high doses (arthritis and rheumatic fever): often increased liver enzymes without symptoms, rarely reversible liver damage. The potentially fatal Reye's syndrome may occur, if given to pediatric patients with fever and other signs of infections. The syndrome is due to fatty degeneration of liver cells. Up to 30 percent of those afflicted will eventually die. Prompt hospital treatment may be life-saving. Chronic nephritis with long-term use, usually if used in combination with certain other painkillers. This condition may lead to chronic renal failure.
- Prolonged and more severe bleeding after operations and post-traumatic for up to 10 days after the last aspirin dose. If one wishes to counteract the bleeding tendency, fresh thrombocyte concentrate will usually work.
- Skin reactions, angioedema, and bronchospasm have all been seen infrequently.

Interactions

Aspirin can interact with some other drugs. Some drugs, for example those used for diabetes, are bound by plasma protein in the blood supply and are therefore not free to react with their targets. However, aspirin may displace them from plasma protein, leading to a drug overdose. Aspirin has this same effect on anticoagulants.

Overdose

Aspirin overdose can be acute or chronic. In acute poisoning, a single large dose is taken; in chronic poisoning, supratherapeutic doses are taken over a period of time. Acute overdose has a mortality rate of 2%. Chronic overdose is more commonly lethal with a mortality rate of 25%; chronic overdose may be especially severe in children.[7]

Symptoms

Aspirin overdose has potentially serious consequences, sometimes leading to significant morbidity and mortality. Patients with mild intoxication frequently have nausea and vomiting, abdominal pain, lethargy, tinnitus, and dizziness. More significant symptoms occur in more severe poisonings and include hyperthermia, tachypnea, respiratory alkalosis, metabolic acidosis, hypokalemia, hypoglycemia, hallucinations, confusion, seizure, cerebral edema, and coma. The most common cause of death following an aspirin overdose is cardiopulmonary arrest usually due to pulmonary edema.[8]

Toxicity

The toxic dose of aspirin is generally considered greater than 150 mg per kg of body mass. Moderate toxicity occurs at doses up to 300 mg/kg, severe toxicity occurs between 300 to 500 mg/kg, and a potentially lethal dose is greater than 500 mg/kg.[9] This is the equivalent of many dozens of the common 325 mg tablets, depending on body weight. Please note that children cannot tolerate as much aspirin per unit body weight as adults can, even when aspirin is indicated. Label-directions should be followed carefully.

Treatment

All overdose patients must be taken to a hospital immediately. Contrary to the urban legend, one can die from ingesting a bottle of pills, even if they are subsequently thrown up.

Initial treatment of an acute overdose includes gastric decontamination of the patient. This is achieved by administering activated charcoal which adsorbs the aspirin in the gastrointestinal tract, stomach pumps are no longer routinely used in the treatment of poisonings but are sometimes considered if the patient has ingested a potentially lethal amount up to 1 hour previously.[10] Repeated doses of charcoal have been proposed to be beneficial in aspirin overdose.[11] A study performed found that repeat dose charcoal might not be of significant value.[12] However, most toxicologists will administer additional charcoal if serum salicylate levels are increasing.

Patients are monitored until their peak salicylate blood level has been determined.[13] Blood levels are usually performed 4 hours after ingestion and then every 2 hours after that to determine the maximum level. Maximum levels can be used as a guide to toxic effects expected.[14]

There is no antidote to salicylate poisoning. Frequent blood work is performed to check metabolic, salicylate, and blood sugar levels; arterial blood gas assessments are performed to test for respiratory alkalosis and metabolic acidosis. Patients are monitored and often treated according to their individual symptoms, patients may be given intravenous potassium chloride to counteract hypokalemia, glucose to restore blood sugar levels, benzodiazepines for any seizure activity, fluids for dehydration, and importantly sodium bicarbonate to restore the blood's sensitive pH balance. Sodium bicarbonate also has the effect of increasing the pH of urine, which in turn increases the elimination of salicylate. Additionally, hemodialysis can be implemented to enhance the removal of salicylate from the blood. Hemodialysis is usually used in severely poisoned patients; for example, patients with significantly high salicylate blood levels, significant neurotoxicity (agitation, coma,

convulsions), renal failure, pulmonary edema, or cardiovascular instability are hemodialyzed.[13] Hemodialysis also has the advantage of restoring electrolyte and acid-base abnormalities; hemodialysis is often life-saving in severely ill patients.

If the overdose was intentional, the patient should undergo psychiatric evaluation, as with any suicide attempt.

Epidemiology

In the later part of the 20th century the number of salicylate poisonings has declined mainly due to the popularity of other over-the-counter analgesics such as paracetamol. Fifty-two deaths involving single-ingredient aspirin were reported in the United States in the year 2000.[15]

Research into cancer prevention

The role that aspirin might have in reducing the rates of certain cancers has been the subject of many studies. However, given the side effects of NSAIDs on increased gastrointestinal bleeding and rates of heart disease, there is no current medical recommendation to use these drugs for cancer reduction.

- *Prostate* - While there is some epidemiological information suggesting a correlation between the reduction of prostate cancer and aspirin use, two recent studies (a multicentric case-control study and epidemiological study) were inconclusive.[16][17]
- *Colon* - A 2005 JAMA article states that aspirin may prevent carcinoma of the colon, when taken in at least twice-daily adult (325 mg) doses.[18] It follows an earlier study, also using the Nurses' Health Study (NHS) women, which had similar conclusions but with a smaller testing population.[19] The conclusions of the studies were that both aspirin and other non-aspirin NSAIDs used over a long time (best results seen after at least a decade of regular use) reduce risk of colorectal cancer. The risk was reduced the most at doses higher than 14 325 mg tablets per week (full-strength aspirin twice a day). However, these doses can have a higher incidence of serious gastrointestinal bleeding, and reduced doses (even the low doses recommended for cardiovascular health (81 mg/day)) also seem to have an anti-cancer effect, albeit not as much as the higher doses.
- *Gall Bladder* - There is some evidence that aspirin may increase gall bladder motility and thus be effective in treating gall bladder disease.
- *Pancreatic* - A study in 2004 showed that increases in dose and duration of aspirin may significantly increase the risk of pancreatic cancer in women (only women were in the study); however this did not seem to affect current, regular users.[20]
- *Upper GI Tract* - A study published in 2003 reported that people who had been taking aspirin regularly for 5 or more years seemed to have a two-thirds less risk of mouth, throat and esophageal cancer than non-users.[21] This study

was done on both cancer patients and other people in hospital for various reasons, and was done by comprehensive epidemiological questionnaires of life habits rather than empirical testing.

- *Lung* - A 20-year study published in 2002 showed that in a group of 14,000 women in New York City, regular aspirin use (defined as at least once a week, various doses) reduced their risk of lung cancer, especially small-cell carcinoma. [22] This may be because many lung tumors have high amounts of COX-2 enzymes expressed in them, especially in adenocarcinomas and tumors caused by asbestosis. [23] Aspirin is a known blocker of both COX-1 and COX-2 enzymes, although this study suggests that if the COX-2 link is direct, other COX-2 inhibitors may also play a similar role. Another study in 2002 of both men and women found that risk reduction was more significant in males than females; overall, the effects of smoking were far more influential than aspirin use in determining cancer risks. [24] Of those who smoked, those who smoked the least got the most benefit from aspirin use. Some of the heaviest smokers saw no benefit from aspirin at all.

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Diclofenac

Systematic (IUPAC) name

*2-[2-(2,6-dichlorophenyl)
aminophenyl]ethanoic acid*

Identifiers

CAS number 15307-86-5

ATC code M01AB05 M02AA15, S01BC03

PubChem 3033

DrugBank APRD00527

Chemical data

Formula $C_{14}H_{11}NCl_2O_2$

Mol. weight 296.148 g/mol

Pharmacokinetic data

Bioavailability **100%**

Protein binding more than 99%

Metabolism hepatic, no active metabolites exist

Half life 1.2-2 hr (35% of the drug enters enterohepatic recirculation)

Excretion biliary, only 1% in urine

Therapeutic considerations

Pregnancy cat. A(AU) B (1st. and 2nd. trimenon), X (third trimenon)

Legal status POM(UK) Rx-only most preparations/countries. Limited OTC some countries

Routes oral, rectal, im, iv (renal- and gallstones), topical

Diclofenac (marketed as *Voltaren*®, *Voltarol*®, *Diclon*®, *Dicloflex*® *Difen*, *Difene*, *Cataflam*® and *Rhumalgan*®) is a non-steroidal anti-inflammatory drug (NSAID) taken to reduce inflammation and an analgesic reducing pain in conditions such as in arthritis or acute injury. It can also be used to reduce menstrual pain.

In the United Kingdom and the United States it may be supplied as either the sodium or potassium salt, while in some other countries only as the potassium salt. Diclofenac is available as a generic drug in a number of formulations. Over the counter (OTC) use is approved in some countries for minor aches and pains and fever associated with common infections.

Diclofenac is well-tolerated after 30 years experience by the general human population, but may unexpectedly become intolerated in some of the elderly population of long term users.

It has been reported that veterinary diclofenac use in India has caused a crash of the vulture population,[1] with "major ecological consequences" and a sub-cultural Zoroastrian Parsi "sky burial" crisis.[2] Diclofenac causes kidney failure in vultures that eat treated domestic animals.

Mechanism of action

The action of one single dose is much longer (6 to 8 hours) than the very short half-life of the drug indicates. This could partly be due to a particular high concentration achieved in synovial fluids.

The exact mechanism of action is not entirely known, but it is thought that the primary mechanism responsible for its anti-inflammatory/antipyretic/analgesic action is inhibition of prostaglandin synthesis by inhibition of cyclooxygenase (COX).

Inhibition of COX also decreases prostaglandins in the epithelium of the stomach, making it more sensitive to corrosion by gastric acid. This is also the main side effect of diclofenac. Diclofenac has a low to moderate preference to block the COX2-isoenzyme (approximately 10-fold) and is said to have therefore a somewhat lower incidence of gastrointestinal complaints than noted with indomethacin and aspirin.

Diclofenac may also be a unique member of the NSAIDs. There is some evidence that diclofenac inhibits the lipooxygenase pathways, thus reducing formation of the leukotrienes (also pro-inflammatory autacoids). There is also speculation that diclofenac may inhibit phospholipase A***2*** as part of its mechanism of action. These additional actions may explain the high potency of diclofenac - it is the most potent NSAID on a molar basis.

There are marked differences among NSAIDs in their selective inhibition of the two subtypes of cyclo-oxygenase, COX-1 and COX-2. Much pharmaceutical drug design has attempted to focus on selective COX-2 inhibition as a way to minimize the gastrointestinal side effects of non-selective NSAIDs like aspirin. In practice, use of some COX-2 inhibitors has led to massive numbers of patient family lawsuits alleging wrongful death by heart attack, yet other significantly COX-selective NSAIDs like diclofenac have been well-tolerated by most of the population.

Indications

Diclofenac is used for musculoskeletal complaints, especially arthritis (rheumatoid arthritis, osteoarthritis, spondylarthritis, ankylosing spondylitis), gout attacks, and pain management in case of kidney stones and gallstones. An additional indication is the treatment of acute migraines. Diclofenac is used commonly to treat mild to moderate post-operative or post-traumatic pain, particular when inflammation is also present, and is effective against menstrual pain.

As long-term use of diclofenac and similar NSAIDs predisposes for peptic ulcer, many patients at risk for this complication are prescribed a combination (Arthrotec®) of

diclofenac and misoprostol, a synthetic prostaglandin analogue, to protect the gastric mucosa.

An external, gel-based form of diclofenac (Solareze®) is available for the treatment of facial actinic keratosis which is caused by over-exposure to sunlight. Some countries have also approved the external use of diclofenac gel to treat muskoskeletal conditions.

Over-the-counter use against minor aches and pains and fever associated with common infections is also licensed in some countries.

In many countries eye-drops are sold to treat acute and chronic non-bacterial inflammations of the anterior part of the eyes (e.g. postoperative states). A common brand name is Voltaren-ophta®.

Off label/investigational uses

Diclofenac is often used to treat chronic pain associated with cancer, particular if inflammation is also present (Step I of the World Health Organisation (WHO) Scheme for treatment of chronic pain). Good results (sometimes better than those with opioids) have been seen in female breast cancer and in the pain associated with bony metastases. Diclofenac can be combined with opioids if needed. In Europe Combaren® exists, a fixed combination of diclofenac and codeine (50 mg each) for cancer treatment. Combinations with psychoactive drugs such as chlorprothixene and/or amitriptyline have also been investigated and found useful in a number of cancer patients.

Fever due to malignant lymphogranulomatosis (Hodgkin's lymphoma) often responds to diclofenac. Treatment can be terminated as soon as the usual treatment with radiation and/or chemotherapy causes remission of fever.

Diclofenac may prevent the development of Alzheimer's disease if given daily in small doses during many years. All investigations were stopped after it was found that some of the other investigated NSAIDs (naproxen, rofecoxib) caused a higher incidence of death cases due to cardiovascular events and stroke compared to placebo.

Diclofenac has been found to increase the blood pressure in patients with Shy-Drager syndrome (autonomous hypotension) often seen in diabetic patients. Currently, this use is highly investigational and cannot be recommended as routine treatment.

Contraindications

- Hypersensitivity against diclofenac
- History of allergic reactions (bronchospasm, shock, rhinitis, urticaria) following the use of Aspirin or another NSAID
- Third-trimester pregnancy
- Active stomach and/or duodenal ulceration or gastrointestinal bleeding
- Inflammative intestinal disorders such as Crohn's disease or ulcerative colitis
- Severe insufficiency of the heart (NYHA III/IV)

- Recently, a warning has been issued by FDA not to treat patients recovering from heart surgery
- Severe liver insufficiency (Child-Pugh Class C)
- Severe renal insufficiency (creatinine clearance <30 ml/min)
- Caution in patients with preexisting hepatic porphyria, as diclofenac may trigger attacks
- Caution in patients with severe, active bleeding such as cerebral hemorrhage

Side effects

- Diclofenac is among the better tolerated NSAIDs. Though 20% of patients on long-term treatment experience side effects, only 2% have to discontinue the drug, mostly due to gastrointestinal complaints.
- Gastrointestinal complaints are most often noted (see above). The development of ulceration and/or bleeding requires immediate termination of treatment with diclofenac. Most patients receive an ulcer-protective drug as prophylaxis during long-term treatment (misoprostol, ranitidine 150mg at bedtime or omeprazole 20 mg at bedtime).
- Bone marrow depression is noted infrequently (leukopenia, agranulocytosis, thrombopenia with/without purpura, aplastic anemia). These conditions may be life-threatening and/or irreversible, if detected too late. All patients should be monitored closely. Diclofenac is a weak and reversible inhibitor of thrombocytic aggregation needed for normal coagulation.
- Liver and renal damage occur infrequently, but are usually reversible. Hepatitis may occur rarely without any warning symptoms and may be fatal. Patients with osteoarthritis develop more often symptomatic liver disease than patients with rheumatoid arthritis. Liver and kidney function should be monitored regularly during long-term treatment. If used for the shortterm treatment of pain or fever, diclofenac has not been found to be more hepatotoxic than other NSAIDs.
- Diclofenac is specifically known to cause kidney failure in Asian vultures. Species and individual humans that are drug sensitive are initially assumed to lack genes expressing specific drug detoxification enzymes. Because elderly humans have reduced expression levels of all enzymes, elderly human metabolisms may gradually approach those of vultures, thus unexpectedly becoming more diclofenac intolerant.
- NSAIDs "are associated with adverse renal [kidney] effects caused by the reduction in synthesis of renal prostaglandins"[3] in sensitive persons or animal species, and potentially during long term use in non-sensitive persons if resistance to side effects decreases with age. Unfortunately this side effect can't be avoided merely by using a COX-2 selective inhibitor because, "Both isoforms of COX, COX-1 and COX-2, are expressed in the kidney... Consequently, the same precautions regarding renal risk that are followed for nonselective NSAIDs should be used when selective COX-2 inhibitors are administered."[3]
- Following the identification of increased risks of heart attacks with the selective COX-2 inhibitor rofecoxib in 2004, attention has focused on all the other members of the NSAIDs group, including Diclofenac. Research results are mixed with a meta-analysis of papers and reports upto April 2006 suggesting a relative increased rate of heart disease of 1.63 compared to non users.[4] Professor Peter Weissberg, Medical Director of the British Heart Foundation said, "However, the increased risk is small and many patients with chronic debilitating pain may well feel that this small risk is worth taking to relieve their symptoms". Only naproxen

was found not to increase the risk of heart disease, however this is known to have a higher rate of gastric ulceration than Diclofenac. A subsequent large study of 74,838 users of NSAIDs or coxibs, published in May 2006 found no additional cardiovascular risk from Diclofenac use.[5]

Formulations

Voltaren and Voltarol contain the sodium salt of diclofenac. In the United Kingdom Voltarol can be supplied with either the sodium salt or potassium salt, while Cataflam in some other countries is the potassium salt only.

Diclofenac is available in stomach acid resistant formulations (25 and 50 mg), fast disintegrating oral formulations (50 mg), slow- and controlled-release forms (75, 100 or 150 mg), suppositories (50 and 100 mg), and injectable forms (50 and 75 mg).

Diclofenac is also available over the counter (OTC) in some countries: Voltaren® dolo (12.5 mg diclofenac as potassium salt) in Switzerland and Germany, and preparations with 25 mg diclofenac are OTC in New Zealand.

Ecological problems

Use of diclofenac in animals has been reported to have led to a sharp decline in the vulture population in the Indian subcontinent, up to 95% in some areas.[6] The mechanism is probably renal failure, a known side-effect of diclofenac. Vultures eat the carcasses of domesticated animals that have been administered veterinary diclofenac, and are poisoned by the accumulated chemical. At a meeting of the National Wildlife Board in March 2005, the Government of India announced that it intended to phase out the veterinary use of diclofenac.[7]Meloxicam is a safer (though more expensive) candidate to replace use of diclofenac.[2]

"The loss of tens of millions of vultures over the last decade has had major ecological consequences across the Indian subcontinent that pose a potential threat to human health. In many places, populations of feral dogs (Canis familiaris) have benefited from the disappearance of Gyps vultures as the main scavenger of wild and domestic ungulate carcasses. Associated with the rise in dog numbers is an increased risk of human cases of rabies."[2]

The Government of India cites one of those major consequences as a vulture species extinction.[7] Westerners may not initially appreciate how a major shift in transfer of corpse pathogens from vultures to feral dogs and rats can lead to a disease pandemic causing millions of deaths in a crowded country like India.

The loss of vultures has had a social impact on the Indian Zoroastrian Parsi community, who traditionally use vultures to dispose of human corpses in "sky burials", and are now having to seek alternative disposal methods.[2]

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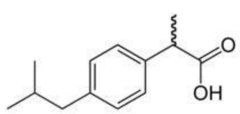
Ibuprofen



Systematic (IUPAC) name

2-[4-(2-methylpropyl)phenyl]propanoic acid

Identifiers

CAS number 15687-27-1

ATC code M01**AE01**

PubChem 3672

DrugBank APRD00372

Chemical data

Formula $C_{13}H_{18}O_2$

Mol. weight 206.3 g/mol

Physical data

Melt. point 76 °C (169 °F)

Pharmacokinetic data

Bioavailability **49–73%**

Protein binding 99%

Metabolism Hepatic

Half life 1.8–2 hours

Excretion Renal

Therapeutic considerations

Pregnancy cat. $C_{(AU)}$ $D_{(US)}$

Legal status $S2_{(AU)}$ $GSL_{(UK)}$ $OTC_{(US)}$

Routes Oral, rectal and topical

Ibuprofen (INN) (IPA: [Èajbjuprof[n]) is a non-steroidal anti-inflammatory drug (NSAID) widely marketed under various trademarks including *Herron Blue*, *Act-3*, *Advil*, *Brufen*, *Motrin*, *Nuprin*, *Dorival* and *Nurofen*. It is used for relief of symptoms of arthritis, primary dysmenorrhoea, fever, and as an analgesic, especially where there is an inflammatory component. Ibuprofen was developed by the research arm of Boots Group.

Clinical use

Low doses of ibuprofen (200 mg, and sometimes 400 mg) are available over the counter (OTC) in most countries. Ibuprofen has a dose-dependent duration of action of approximately 4–8 hours, which is longer than suggested by its short half-life. The recommended dose varies with body mass and indication. Generally, the oral dose is 200–400 mg (5–10 mg/kg in children) every 4–6 hours, up to a usual maximum daily dose of 800–1200 mg. Under medical direction, a maximum daily dose of 3200 mg may sometimes be used.

Off-Label and investigational use

- As with other NSAIDs, ibuprofen may be useful in the treatment of severe orthostatic hypotension.[1]

- In some studies, ibuprofen showed superior results compared to placebo in the prophylaxis of Alzheimer's disease, when given in low doses over a long time.[2] Further studies are needed to confirm the results before ibuprofen can be recommended for this indication.
- Ibuprofen has been associated with a lower risk of Parkinson's disease, and may delay or prevent Parkinson's disease. Aspirin, other NSAIDs, and paracetamol had no effect on the risk for Parkinson's.[3] Further research is warranted before recommending ibuprofen for this use.

Ibuprofen lysine

In Europe, Australia, and New Zealand, *ibuprofen lysine* (ibuprofenlysinat, the lysine salt of ibuprofen) is licensed for treatment of the same conditions as ibuprofen. Ibuprofen lysine has been shown to have a more rapid onset of action compared to base ibuprofen.[4]

Mechanism of action

Ibuprofen is an NSAID which is believed to work through inhibition of cyclooxygenase (COX), thus inhibiting prostaglandin synthesis. There are at least 2 variations of cyclooxygenase (COX-1 and COX-2), ibuprofen inhibits both COX-1 and COX-2. It appears that its analgesic, antipyretic, and anti-inflammatory activity are achieved principally through COX-2 inhibition; whereas COX-1 inhibition is responsible for its unwanted effects on platelet aggregation and the GI mucosa.

Main article: Non-steroidal anti-inflammatory drug

Adverse effects

Ibuprofen appears to have the lowest incidence of gastrointestinal adverse drug reactions (ADRs) of all the non-selective NSAIDs. However, this only holds true at lower doses of ibuprofen, so over-the-counter preparations of ibuprofen are generally labelled to advise a maximum daily dose of 1,200 mg.

Main article: Non-steroidal anti-inflammatory drug

Reported adverse drug reactions

In low single doses (200 to 400 mg) and daily doses of up to 1,200 mg the incidence of side effects is low. However, in patients treated on a long-term basis with more than 1,200 mg daily discontinuation rates are as high as 10 to 15%.

Common adverse effects include: nausea, dyspepsia, gastrointestinal ulceration/bleeding, raised liver enzymes, diarrhea, headache, dizziness, salt and fluid retention, hypertension.[5]

Infrequent adverse effects include: oesophageal ulceration, heart failure, hyperkalaemia, renal impairment, confusion, bronchospasm, rash.[5]

Photosensitivity

As with other NSAIDs, ibuprofen has been reported to be a photosensitising agent.[6][7] However, this only rarely occurs with ibuprofen and it is considered to be a very weak photosensitising agent when compared with other members of the 2-arylpropionic acids. This is because the ibuprofen molecule contains only a single phenyl moiety and no bond conjugation, resulting in a very weak chromophore system and a very weak absorption spectrum which does not reach into the solar spectrum.

Cardiovascular risk

Along with several other NSAIDs, ibuprofen has been implicated in elevating the risk of myocardial infarction, particularly among those chronically using high doses.[8]

Stereochemistry

Ibuprofen, like other 2-arylpropionate derivatives (including ketoprofen, flurbiprofen, naproxen, etc) contains a chiral carbon in the ±-position of the propionate moiety. As such there are two possible enantiomers of ibuprofen with the potential for different biological effects and metabolism for each enantiomer.

Indeed it was found that (S)-(+)-ibuprofen (dexibuprofen) was the active form both in vitro and in vivo.

It was logical, then, that there was the potential for improving the selectivity and potency of ibuprofen formulations by marketing ibuprofen as a single-enantiomer product (as occurs with naproxen, another NSAID.).

Further in vivo testing, however, revealed the existence of an isomerase which converted (R)-ibuprofen to the active (S)-enantiomer. Thus, due to the expense and futility that might be involved in marketing the single-enantiomer, most ibuprofen formulations currently marketed are racemic mixtures. A notable exception to this is *Seractiv* (Nordic Drugs).

Human toxicology

Ibuprofen overdose has become common since it was licensed for over-the-counter use. There are many overdose experiences reported in the medical literature.[9] Human response in cases of overdose ranges from absence of symptoms to fatal outcome in spite of intensive care treatment. Most symptoms are an excess of the pharmacological action of ibuprofen and include abdominal pain, nausea, vomiting, drowsiness, dizziness, headache, tinnitus, and nystagmus. Rarely more severe symptoms such as gastrointestinal bleeding, seizures, metabolic acidosis, hyperkalaemia, hypotension, bradycardia, tachycardia, atrial fibrillation, coma, hepatic dysfunction, acute renal failure, cyanosis, respiratory depression, and cardiac arrest have been reported.[10]. The severity of symptoms varies with the ingested dose and the time elapsed, however, individual sensitivity also plays an important role. Generally, the symptoms observed with an overdose of ibuprofen are similar to the symptoms caused by overdoses of other NSAIDs.

There is little correlation between severity of symptoms and measured ibuprofen plasma levels. Toxic effects are unlikely at doses below 100 mg/kg but can be severe above 400 mg/kg;[11] however, large doses do not indicate that the clinical course is likely to be lethal.[12] It is not possible to determine a precise lethal dose, as this may vary with age, weight, and concomitant diseases of the individual patient.

Therapy is largely symptomatic. In cases presenting early, gastric decontamination is recommended. This is achieved using activated charcoal; charcoal absorbs the drug before it can enter the systemic circulation. Gastric lavage is now rarely used, but can be considered if the amount ingested is potentially life threatening and it can be performed within 60 minutes of ingestion. Emesis is not recommended.[13] The majority of ibuprofen ingestions produce only mild effects and the management of overdose is straightforward. Standard measures to maintain normal urine output should be instituted and renal function monitored.[11] Since ibuprofen has acidic properties and is also excreted in the urine, forced alkaline diuresis is theoretically beneficial. However, due to the fact ibuprofen is highly protein bound in the blood, there is minimal renal excretion of unchanged drug. Forced alkaline diuresis is therefore of limited benefit.[14] Symptomatic therapy for hypotension, GI bleeding, acidosis, and renal toxicity may be indicated. Occasionally, close monitoring in an intensive care unit for several days is necessary. If a patient survives the acute intoxication, he/she will usually experience no late sequelae.

Availability

Ibuprofen was made available under prescription in the United Kingdom in 1969. In the years since, the good tolerability profile along with extensive experience in the community (otherwise known as Phase IV trials), has resulted in the rescheduling of small packs of ibuprofen to allow availability over-the-counter in pharmacies worldwide. Indeed there has been an increasing trend towards descheduling ibuprofen such that it is now available in supermarkets and other general retailers. The wider availability has meant that ibuprofen is now almost as commonly used as aspirin and paracetamol.

See also

- Paracetamol

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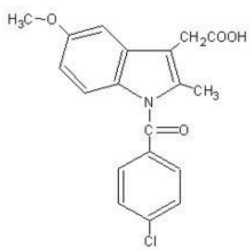
Indometacin



Systematic (IUPAC) name

1-(4-chlorobenzoyl)-5-methoxy-
2-methyl-1-H-indole-3-acetic acid

Identifiers

CAS number 53-86-1

ATC code C01**EB03** M01**AB01**, M02**AA23**, S01**BC01**

PubChem 3715

DrugBank APRD00109

Chemical data

Formula $C_{19}H_{16}NClO_4$

Mol. weight 357.79 g.mol-1

Pharmacokinetic data

Bioavailability ~100% (oral), 80–90% (rectal)

Protein binding 99%

Metabolism Hepatic

Half life 4.5 hours

Excretion Renal 60%, faecal 33%

Therapeutic considerations

Pregnancy cat. C (Au), C/D (US)

***Legal status P**rescription only*

Routes Oral, rectal, IV, topical

Indometacin (INN) or *Indomethacin* (USAN and former BAN) is a non-steroidal anti-inflammatory drug commonly used to reduce fever, pain, stiffness, and swelling. It works by inhibiting the production of prostaglandins, molecules known to cause these symptoms. It is marketed under many trade names, including *Indocin*, *Indocid*, *Indochron E-R*, and *Indocin-SR*.

Chemical properties

Indometacin is a methylated indole derivative and a member of the arylalkanoic acid class of NSAIDs, which includes diclofenac.

Indications

Clinical indications for indometacin include:

- ankylosing spondylitis
- rheumatoid arthritis
- arthritic gout
- osteoarthritis
- juvenile arthritis
- psoriatic arthritis
- Reiter's syndrome
- Paget's disease of bone
- Bartter syndrome
- pseudogout
- dysmenorrhea (menstrual cramps)
- pericarditis
- bursitis
- tendinitis
- nephrogenic diabetes insipidus (prostaglandin inhibits vasopressin's action in the kidney)
- fever and pain associated with malignant diseases (tumors, bony metastases, lymphogranulomatosis)
- Paroxysmal hemicrania, hemicrania continua and migraine

Indometacin has also been used clinically to delay premature labor, reduce amniotic fluid in polyhydramnios, and to treat patent ductus arteriosus.

Indometacin is a potent drug with many serious side effects and should not be considered an analgesic for minor aches and pains or fever. The drug is more potent than aspirin, but is not a better analgesic. In mild to moderate pain a standard oral dose of indometacin proved as effective as 600mg aspirin.

Contraindications

- concurrent peptic ulcer, or history of ulcer disease
- allergy to indometacin, aspirin, or other NSAIDs
- patients with nasal polyps reacting with an angioedema to other NSAIDs
- children under 2 years of age (with the exception of neonates with patent ductus arteriosus)
- severe preexisting renal and liver damage
- caution : preexisting bone marrow damage (frequent blood cell counts are indicated)

caution : bleeding tendencies of unknown origin (indometacin inhibits platelet aggregation)
caution : Parkinson's disease, epilepsy, psychotic disorders (indometacin may worsen these conditions)

Mechanism of action

Main article: Non-steroidal anti-inflammatory drug

Indometacin is a nonselective inhibitor of cyclooxygenase (COX) 1 and 2, enzymes that participate in prostaglandin synthesis from arachidonic acid. Prostaglandins are hormone-like molecules normally found in the body, where they have a wide variety of effects, some of which lead to pain, fever, and inflammation.

Prostaglandins also cause uterine contractions in pregnant women. Indometacin is an effective tocolytic agent, able to delay premature labor by reducing uterine contractions through inhibition of PG synthesis in the uterus and possibly through calcium channel blockade.

Indometacin has two additional modes of actions with clinical importance:

- It inhibits motility of polymorphonuclear leucocytes, similar to colchicine.
- It uncouples oxidative phosphorylation in cartilaginous (and hepatic) mitochondria, like salicylates.

These additional effects account as well for the analgesic and the anti-inflammatory properties.

Indometacin readily crosses the placenta, and can reduce fetal urine production to treat polyhydramnios. It does so by reducing renal blood flow and increasing renal vascular resistance, possibly by enhancing the effects of vasopressin on the fetal kidneys.

Adverse effects

Since indometacin inhibits both COX-1 and COX-2, it inhibits the production of prostaglandins in the stomach and intestines which maintain the mucous lining of the gastrointestinal tract. Indometacin, therefore, like other nonselective COX inhibitors, can cause peptic ulcers. The ulcers can result in serious bleeding and/or perforation requiring hospitalization of the patient. Some even die from these complications. To reduce the possibility of peptic ulcers, indometacin should be prescribed at the lowest dosage needed to achieve a therapeutic effect, usually between 50–200 mg/day. It should always be taken with food. Nearly all patients benefit from an ulcer protective drug (e.g. highly dosed antacids, ranitidine 150mg at bedtime, or omeprazole 20mg at bedtime). Other common gastrointestinal complaints, including dyspepsia, heartburn and mild diarrhea are less serious and rarely require discontinuation of indometacin.

Many NSAIDs, but particularly indometacin, cause lithium retention by reducing its excretion by the kidneys. Thus indometacin users have an elevated risk of lithium toxicity. For patients taking lithium supplements (e.g. for treatment of depression or bipolar disorder), less toxic NSAIDs such as sulindac or aspirin, are preferred.

Indometacin also reduces plasma renin activity and aldosterone levels, and increases sodium and potassium retention. It also enhances the effects of vasopressin. Together these may lead to:

- edema (swelling due to fluid retention)
hyperkalemia (high potassium levels)
hypernatremia (high sodium levels)
hypertension (high blood pressure)

The drug may also cause elevations of serum creatinine and more serious renal damage such as acute renal failure, chronic nephritis and nephrotic syndrome. These conditions also often begin with edema and hyperkalema.

Additionally, indometacin quite often causes headache (10 to 20%), sometimes with vertigo and dizziness, hearing loss, tinnitus, blurred vision (with or without retinal damage) and worsens Parkinson's disease, epilepsy, and psychiatric disorders. Cases of life-threatening shock (including angioedema, sweating, severe hypotension and tachycardia as well as acute bronchospasm), severe or lethal hepatitis and severe bone marrow damage have all been reported. Skin reactions and photosensitivity are also possible side effects.

Due to its strong antipyretic activity indometacin may obscure the clinical course of serious infections.

The frequency and severity of side effects and the availability of better tolerated alternatives make indometacin today a drug of second choice. Its use in acute gout attacks and in dysmenorrhea is well-established because in these indications the duration of treatment is limited to a few days only, therefore serious side effects are not likely to occur.

Necessary Examinations during Longterm Treatment

Patients should undergo regular physical examination to detect edema and signs of central nervous side effects. Blood presssure checks will reveal development of hypertension. Periodic serum electrolyte (sodium, potassium, chloride) measurements, complete blood cell counts and assessment of liver enzymes as well as of creatinine (renal function) should be performed. This is particularly important if indometacin is given together with an ACE inhibitor or with potassium-sparing diuretics, because these combinations can lead to hyperkalemia and/or serious kidney failure. No examinations are necessary if only the topical preparations (spray or gel) are applied.

Animal Toxicity and Human Overdose

Indomethacin has a high acute toxicity both for animals (12 mg/kg in rats and 50 mg/kg in mice) and for humans. Exact human data does not exist, but some fatal human cases, particularly in children and adolescents, have been seen.

Generally, overdose in humans causes drowsiness, dizziness, severe headache, mental confusion, paraesthesia, numbness of limbs, nausea and vomiting. Severe gastrointestinal bleeding is also possible. Cerebral edema, and cardiac arrest with fatal outcome have been seen in children.

The treatment is symptomatic and largely the same as with diclofenac. However, the possibility of severe GI tract symptoms should be particularly noted.

The risk of overdose after exaggerated local treatment with gel or spray is very limited.

Usual Dosage Forms

- Tablets or Capsules 25 and 50mg
- Suppositories 50 and 100mg
- Modified-release Capsules 75mg
- Syrup (25mg/5ml)
- Injectable concentrate 50mg for i.m. injection
- Spray or Gel
- Patches containing 0.5% by weight
- 1% topical liquid

History

Indometacin was discovered in 1963 and it was first approved for use in the U.S. by the Food and Drug Administration in 1965. Its mechanism of action, along with several other NSAIDs that inhibit COX, was described in 1971.

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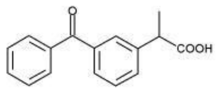
Ketoprofen



Systematic (IUPAC) name

2-(3-benzoylphenyl)propanoic acid

Identifiers

CAS number 22071-15-4

ATC code M01**AE03** M01**AE17**, M02**AA10**

PubChem 3825

DrugBank APRD01059

Chemical data

Formula C***16***H***14***O***3***

Mol. weight 254.281 g/mol

Pharmacokinetic data

Protein binding 99%

Half life 2-2.5 hours

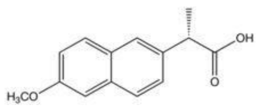
Ketoprofen, *(RS)2-(3-benzoylphenyl)-propionic acid* (chemical formula C***16***H***14***O***3***) is one of the propionic acid class of non-steroidal anti-inflammatory drug (NSAID) with analgesic and antipyretic effects. It acts by inhibiting the body's production of prostaglandin.

Ketoprofen was available over-the-counter in the United States in the form of 12.5mg coated tablets (Orudis KT®), but the product has been discontinued. It is available by prescription as 25, 50, 75, 100, 150, and 200mg capsules.

Ketoprofen also comes in a 2,5% gel for topical application.

Brand names in the US are *Orudis* and *Oruvail*.

Naproxen



Systematic (IUPAC) name

(+)-(S)-2-(6-methoxynaphthalen-2-yl) propanoic acid

Identifiers

CAS number 22204-53-1

ATC code G02**CC02** M01**AE02**, M02**AA12**

PubChem 1302

DrugBank APRD01135

Chemical data

Formula $C_{14}H_{14}O_3$

Mol. weight 230.259 g/mol

Pharmacokinetic data

Bioavailability **95% (oral)**

Protein binding 99%

Metabolism Hepatic (to 6-desmethylnaproxen)

Half life 12–15 hours

Excretion Renal

Therapeutic considerations

Pregnancy cat. $C_{(AU)}$ $B_{(US)}$

Legal status $S2_{(AU)}$ $POM_{(UK)}$ $OTC_{(US)}$

-only(Ca)

Routes Oral

Naproxen (INN) (IPA: [nYÈprRksYn]) is a non-steroidal anti-inflammatory drug (NSAID) commonly used for the reduction of mild to moderate pain, fever, inflammation and stiffness caused by conditions such as osteoarthritis, rheumatoid arthritis, psoriatic arthritis, gout, ankylosing spondylitis, injury (like fractures), menstrual cramps, tendonitis, bursitis, and the treatment of primary dysmenorrhea. Naproxen and *naproxen sodium* are marketed under various trade names including: *Aleve*, *Anaprox*, *Naprogesic*, *Naprosyn*, *Naprelan*.

Naproxen was first marketed as the prescription drug Naprosyn in 1976 and naproxen sodium was first marketed under the trade name Anaprox in 1980. It remains a prescription-only drug in much of the world. The U.S. Food and Drug Administration (FDA) approved the use of naproxen sodium as an over-the-counter (OTC) drug in 1991, where OTC preparations are sold under the trade name Aleve. In Australia, small packets of lower-strength preparations of naproxen sodium are Schedule 2 Pharmacy Medicines.

Structure and details

Naproxen is a member of the 2-arylpropionic acid (profen) family of NSAIDs. It is an odorless, white to off-white crystalline substance. It is lipid-soluble, practically insoluble in water with a low pH (below pH 4), while freely soluble in water at 6 pH and above. Naproxen has a melting point of 153 °C.

Adverse effects and warnings

Like other NSAIDs, naproxen is capable of producing disturbances in the gastrointestinal tract. Taking the medication with food may help to alleviate this most commonly reported adverse effect.

Also like other NSAIDs, naproxen can inhibit the excretion of sodium and lithium. Extreme care must be taken by those who use this drug along with lithium supplements.

Naproxen is also not recommended for use with NSAIDs of the salicylate family (drugs may reduce each other's effects), nor with anticoagulants (may increase risk of bleeding).

Certain preparations of Naproxen are not recommended for use in patients with hypertension, as they contain sodium, worsening the effects of hypertension.

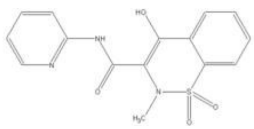
In August 2006, the journal Birth Defects Research Part B published results in the September issue indicating that pregnant women who take NSAIDs including Naproxen in the first trimester run an increased risk of having a child with congenital birth defects, particularly heart anomalies.

In December 2004, the FDA issued a press release following the decision by the National Institutes of Health to halt a five-year study, called the Alzheimer's Disease Anti-Inflammatory Prevention Trial. That study aimed to test both Aleve and Celebrex as preventives for Alzheimer's disease. Preliminary information from the study showed naproxen elevated the risk of heart attack and stroke by 50%. The FDA advised patients taking over-the-counter naproxen products to:

- carefully follow the instructions on the label,
- avoid exceeding the recommended doses for naproxen (220 milligrams twice daily), and

- take naproxen for no longer than ten days unless a physician directs otherwise.

Piroxicam



Systematic (IUPAC) name

9-(hydroxy-pyridin-2-ylamino-methylidene)- 8-methyl-7,7-dioxo-7$l^{6}-thia-8-azabicyclo[4.4.0] deca-1,3,5-trien-10-one

Identifiers

CAS number 36322-90-4

ATC code M01**AC01** M02**AA07**, S01**BC06**

PubChem 5280452

DrugBank APRD01187

Chemical data

Formula $C_{15}H_{13}N_{3}O_{4}S$

Mol. weight 331.348 g/mol

Pharmacokinetic data

Metabolism 4-10% renal

Half life 30 to 86 hours

Excretion 4-10% renal

Therapeutic considerations

Pregnancy cat. C, D if used in the third trimester or near delivery

Piroxicam (US trade name *Feldene*) is a nonsteroidal anti-inflammatory drug used to relieve the symptoms of arthritis, primary dysmenorrhoea, pyrexia; and as an analgesic, especially where there is an inflammatory component. It is also used in veterinary medicine

to treat certain neoplasias expressing cyclooxygenase (COX) receptors, such as bladder, colon, and prostate cancers.

Mechanism of action

Main article: Non-steroidal anti-inflammatory drug

Piroxicam is an NSAID and, as such, is a non-selective COX inhibitor possessing both analgesic and antipyretic properties.

Adverse effects

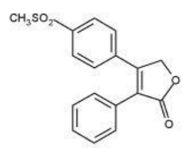
Main article: Non-steroidal anti-inflammatory drug

Piroxicam use can result in gastrointestinal toxicity, tinnitus, dizziness, headache, rash, and pruritus. The most severe adverse reactions are peptic ulceration and gastrointestinal bleeding. Approximately 30% of all patients receiving daily doses of 20 mg of piroxicam experience side effects.[1]

Footnotes

1. ^ New Zealand Medicines and Medical Devices Safety Authority. Candyl Medicines datasheet. Retrieved on 2006-09-10.

Rofecoxib



Systematic (IUPAC) name

4-(4-methylsulfonylphenyl)-3-phenyl-5H-furan-2-one

Identifiers

CAS number 162011-90-7

ATC code M01**AH02**

PubChem 5090

DrugBank APRD00151

Chemical data

Formula C***17***H***14***O***4***S

Mol. weight 314.357 g/mol

Pharmacokinetic data

Bioavailability **93%**

Protein binding 87%

Metabolism hepatic

Half life 17 hours

Excretion biliary/renal

Therapeutic considerations

Pregnancy cat. C (Australia)

Legal status withdrawn

Routes oral

Rofecoxib (IPA: [rofYÈkRksjb]) is a nonsteroidal anti-inflammatory drug (NSAID) developed by Merck & Co. to treat osteoarthritis, acute pain conditions, and dysmenorrhoea. Rofecoxib was approved safe and effective by the Food and Drug Administration (FDA) on May 20, 1999 and was subsequently marketed under the brand name *Vioxx*, *Ceoxx* and *Ceeoxx*.

Rofecoxib gained widespread acceptance among physicians treating patients with arthritis and other conditions causing chronic or acute pain. Worldwide, over 80 million people were prescribed rofecoxib at some time.

On September 30, 2004, Merck voluntarily withdrew rofecoxib from the market because of concerns about increased risk of heart attack and stroke. Rofecoxib was one of the most widely used drugs ever to be withdrawn from the market. In the year before withdrawal, Merck had sales revenue of US$2.5 billion from Vioxx.(need source)

Rofecoxib was available on prescription as tablets and as an oral suspension.

Non-Steroidal Anti-Inflammatory Drugs

Rofecoxib belongs to a class of pain relievers called non-steroidal anti-inflammatory drugs or NSAIDS. This class includes many medications sold either over the counter – such as ibuprofen (Advil) and naproxen (Aleve) or by prescription – such as oxaprozin (Daypro) and diclofenac (Voltaren). Like aspirin, which is sometimes classified as an NSAID, traditional NSAIDS work by inhibiting cyclooxygenase (COX), an enzyme that stimulates the synthesis of prostaglandins, chemicals in the body that promote inflammation and pain.

While traditional NSAIDS have long been a mainstay of treatment for patients needing pain relief, this relief does not come without significant adverse side effects—namely a great increase in the risk of gastrointestinal perforations, ulcers, and bleeds or PUBs. Scientists have estimated that NSAID-induced PUBs have caused more than 16,500 deaths and 100,000 hospitalizations annually in the United States. (Wolfe, MM et al, 1999)

The COX Enzyme

In the early 1990s, scientists discovered that the COX enzyme had two forms, now called COX-1 and COX-2. COX-1 mediated the synthesis of prostaglandins responsible for protection of the stomach lining, while COX-2 mediated the synthesis of prostaglandins responsible for pain and inflammation. By creating "selective" NSAIDS that inhibit COX-2, but not COX-1, scientists hypothesized they could offer the same pain relief as traditional NSAIDS, but with greatly reduced risk of fatal or debilitating PUBs.

Rofecoxib is a selective COX-2 inhibitor or coxib (CycloOXygenase-2 InhiBitors). Others include Pfizer's celecoxib (Celebrex) and valdecoxib (Bextra). Interestingly, at the time of its withdrawal, rofecoxib was the only coxib with clinical evidence of its superior gastrointestinal adverse effect profile over conventional NSAIDs. This was largely based on the VIGOR (Vioxx GI Outcomes Research) study, which compared the efficacy and adverse effect profiles of rofecoxib and naproxen. (Bombardier et al., 2000).

Adverse drug reactions

Main article: Non-steroidal anti-inflammatory drug

Aside from the reduced incidence of gastric ulceration, rofecoxib exhibits a similar adverse effect profile to other NSAIDs. Rofecoxib, however, does appear to increase the risk of adverse cardiovascular events (see below).

The chief mechanism proposed to explain rofecoxib's cardiotoxicity is the suppression of prostaglandin, an anti-clotting agent in the blood (Fitzgerald, 2004). COX-2 plays a role in the production of prostaglandin. Because Vioxx inhibits the COX-2 enzyme, prostaglandin production can decrease in endothelial cells and lead to an inefficiency in declumping and vasorelaxtion. Merck, however, argues that there was no effect on prostaglandin production in blood vessels in animal testing] Other researchers have speculated that the cardiotoxicity may be associated with maleic anhydride metabolites formed when rofecoxib becomes ionised under physiological conditions. (Reddy & Corey, 2005)

Vioxx has also been associated with cardiovascular disease, renal (kidney) disease, and heart arrhythmia.

Withdrawal from the market

VIGOR study

The VIGOR (Vioxx GI Outcomes Research) study, which compared the efficacy and adverse effect profiles of rofecoxib and naproxen. (Bombardier et al., 2000), had indicated a

significant 4-fold increased risk of acute myocardial infarction (heart attack) in rofecoxib patients when compared with naproxen patients (0.4% vs 0.1%, RR 0.25) over the 12 month span of the study. The elevated risk began during the second month on rofecoxib. There was no significant difference in the mortality from cardiovascular events between the two groups. Nor was there any significant difference in the rate of myocardial infarction between the rofecoxib and naproxen treatment groups in patients without high cardiovascular risk. The difference in overall risk was accounted for by the patients at higher risk of heart attack: those meeting the criteria for low-dose aspirin prophylaxis of secondary cardiovascular events (previous myocardial infarction, angina, cerebrovascular accident, transient ischemic attack, or coronary artery bypass). (Bombardier et al., 2000)

Merck's scientists interpreted the finding as a protective effect of naproxen, telling the FDA that the difference in heart attacks "is primarily due to" this protective effect (Targum, 2001). Some commentators have noted that naproxen would have to be three times as effective as aspirin to account for all of the difference (Michaels 2005), and some outside scientists warned Merck that this claim was implausible before VIGOR was published. No evidence has since emerged for such a large cardioprotective effect of naproxen, although a number of studies have found protective effects similar in size to those of aspirin (Karha and Topol, 2004; Solomon et al., 2002). Though Dr. Topol's 2004 paper criticized Merck's naproxen hypothesis, he himself co-authored a 2001 JAMA article stating "because of the evidence for an antiplatelet effect of naproxen, it is difficult to assess whether the difference in cardiovascular event rates in VIGOR was due to a benefit from naproxen or to a prothrombotic effect from rofecoxib." (Mukherjee, Nissen and Topol, 2001.)

The results of the VIGOR study were submitted to the United States Food and Drug Administration (FDA) in February 2001, which led to the introduction, in April 2002, of warnings on Vioxx labelling concerning the increased risk of cardiovascular events (heart attack and stroke).

NEJM controversy

Months after the preliminary version of VIGOR was published in the New England Journal of Medicine, the journal editors learned that certain data reported to the FDA was not included in the NEJM article. Several years later, when they were shown a Merck memo during the depositions for the first federal Vioxx trial, they realized that this data had been available to the authors months before publication. The editors wrote an editorial accusing the authors of deliberately withholding the data (Curfman et al, 2006a). They released the editorial to the media on December 8, 2005, before giving the authors a chance to respond. NEJM editor Gregory Curfman explained that the quick release was due to the imminent presentation of his deposition testimony, which he feared would be misinterpreted in the media. He had earlier denied any relationship between the timing of the editorial and the trial. Although his testimony was not actually used in the December trial, Curfman had testified well before the publication of the editorial.

The editors charged that "more than four months before the article was published, at least two of its authors were aware of critical data on an array of adverse cardiovascular events that were not included in the VIGOR article." This additional data included three

additional heart attacks, and raised the relative risk of Vioxx from 4.25-fold to 5-fold. All the additional heart attacks occurred in the group at low risk of heart attack (the "aspirin not indicated" group) and the editors noted that the omission "resulted in the misleading conclusion that there was a difference in the risk of myocardial infarction between the aspirin indicated and aspirin not indicated groups." The relative risk for myocardial infarctions among the aspirin not indicated patients increased from 2.25 to 3 (although it remained statitistically insignificant). The editors also noted a statistically significant (2-fold) increase in risk for serious thromboembolic events for this group, an outcome that Merck had not reported in the NEJM, though it had disclosed that information publicly in March 2000, eight months before publication. (Curfman et al., 2006b, Supplementary Material).

The authors of the study, including the non-Merck authors, responded by claiming that the three additional heart attacks had occurred after the prespecified cutoff date for data collection and thus were appropriately not included. (Utilizing the prespecified cutoff date also meant that an additional stroke in the naproxen population was not reported.) Furthermore, they said that the additional data did not qualitatively change any of the conclusions of the study, and the results of the full analyses were disclosed to the FDA and reflected on the Vioxx warning label. They further noted that all of the data in the "omitted" table was printed in the text of the article. The authors stood by the original article. (Bombardier et al., 2006).

NEJM stood by its editorial, noting that the cutoff date was never mentioned in the article, nor did the authors report that the cutoff for cardiovascular adverse events was before that for gastrointestinal adverse events. The different cutoffs increased the reported benefits of Vioxx (reduced stomach problems) relative to the risks (increased heart attacks). (Curfman et al., 2006b).

Some scientists have accused the NEJM editorial board of making unfounded accusations. Others have applauded the editorial. Renowned research cardiologist Eric Topol, a prominent Merck critic, accused Merck of "manipulation of data" and said "I think now the scientific misconduct trail is really fully backed up". Phil Fontanarosa, executive editor of the prestigious Journal of the American Medical Association, welcomed the editorial, saying "this is another in the long list of recent examples that have generated real concerns about trust and confidence in industry-sponsored studies"

Alzheimer's studies

In 2000 and 2001, Merck conducted several studies of rofecoxib aimed at determining if the drug slowed the onset of Alzheimer's disease. Merck has placed great emphasis on these studies on the grounds that they are relatively large (almost 3000 patients) and compared rofecoxib to a placebo rather than to another pain reliever. These studies found an elevated death rate among rofecoxib patients, although the deaths were not generally heart-related. However, they did not find any elevated cardiovascular risk due to rofecoxib (Konstam et al., 2001). Before 2004, Merck cited these studies as providing evidence, contrary to VIGOR, of rofecoxib's safety.

APPROVe study

In 2001, Merck commenced the APPROVe (Adenomatous Polyp PRevention On Vioxx) study, a three year trial with the primary aim of evaluating the efficacy of rofecoxib for the prophylaxis of colorectal polyps. Celecoxib had already been approved for this indication, and it was hoped to add this to the indications for rofecoxib as well. An additional aim of the study was to further evaluate the cardiovascular safety of rofecoxib.

The APPROVe study was terminated early when the preliminary data from the study showed an increased relative risk of adverse thrombotic cardiovascular events (including heart attack and stroke), beginning after 18 months of rofecoxib therapy. In patients taking rofecoxib, versus placebo, the relative risk of these events was 1.92 (rofecoxib 1.50 events vs placebo 0.78 events per 100 patient years). The results from the first 18 months of the APPROVe study did not show an increased relative risk of adverse cardiovascular events. Moreover, overall and cardiovascular mortality rates were similar between the rofecoxib and placebo populations. (Bresalier et al., 2005)

In sum, the APPROVe study suggested that long-term use of rofecoxib resulted in nearly twice the risk of suffering a heart attack or stroke compared to patients receiving a placebo.

Other studies

Pre-approval Phase III clinical trials, like the APPROVe study, showed no increased relative risk of adverse cardiovascular events for the first eighteen months of rofecoxib usage (Merck, 2004). Others have pointed out that "study 090," a pre-approval trial, showed a 3-fold increase in cardiovascular events compared to placebo, a 7-fold increase compared to nabumetone (another [NSAID]), and an 8-fold increase in heart attacks and strokes combined compared to both control groups. Although this was a relatively small study and only the last result was statistically significant, critics have charged that this early finding should have prompted Merck to quickly conduct larger studies of Merck's cardiovascular safety. Merck notes that it had already begun VIGOR at the time Study 090 was completed. Although VIGOR was primarily designed to demonstrate new uses for rofecoxib, it also collected data on adverse cardiovascular outcomes.

Several very large observational studies have also found elevated risk of heart attack from rofecoxib. For example, a recent retrospective study of 113,000 elderly Canadians suggested a borderline statistically significant increased relative risk of heart attacks of 1.24 from Vioxx usage, with a relative risk of 1.73 for higher-dose Vioxx usage. (Levesque, 2005). Another study, using Kaiser Permanente data, found a 1.47 relative risk for low-dose Vioxx usage and 3.58 for high-dose Vioxx usage compared to current use of celecoxib, though the smaller number was not statistically significant, and relative risk compared to other populations was not statistically significant. (Graham, 2005).

Furthermore, a more recent study of 114 randomized trial comprised of 116,000+ participants, published in JAMA, showed that Vioxx uniqued increased risk of renal (kidney) disease, and heart arrhythmia.

Withdrawal

Merck publicly announced its voluntary withdrawal of the drug from the market worldwide on September 30, 2004.

In addition to its own studies, on September 23, 2004 Merck apparently received information about new research by the FDA that supported previous findings of increased risk of heart attack among rofecoxib users (Grassley, 2004). FDA analysts estimated that Vioxx caused between 88,000 and 139,000 heart attacks, 30 to 40 percent of which were probably fatal, in the five years the drug was on the market.

On November 5 the medical journal The Lancet published a meta-analysis of the available studies on the safety of rofecoxib (Jüni et al., 2004). The authors concluded that, owing to the known cardiovascular risk, rofecoxib should have been withdrawn several years earlier. The Lancet published an editorial which condemned both Merck and the FDA for the continued availability of rofecoxib from 2000 until the recall. Merck responded by issuing a rebuttal of the Jüni et al. meta-analysis that noted that Juni omitted several studies that showed no increased cardiovascular risk. (Merck & Co., 2004).

In 2005, advisory panels in both the U.S. and Canada encouraged the return of rofecoxib to the market, stating that rofecoxib's benefits outweighed the risks for some patients. The FDA advisory panel voted 17-15 to allow the drug to return to the market despite being found to increase heart risk. The vote in Canada was 12-1, and the Canadian panel noted that the cardiovascular risks from rofecoxib seemed to be no worse than those from ibuprofen -- though the panel recommended that further study was needed for all NSAIDs to fully understand their risk profiles. Notwithstanding these recommendations, Merck has not returned rofecoxib to the market.

Litigation

As of March 2006, there had been over 10,000 cases and 190 class actions filed against Merck over adverse cardiovascular events associated with rofecoxib and the adequacy of Merck's warnings. The first wrongful death trial, Rogers v. Merck, was scheduled in Alabama in the spring of 2005, but was postponed after Merck argued that the plaintiff had falsified evidence of rofecoxib use.

On August 19, 2005, a jury in Texas voted 10-2 to hold Merck liable for the death of Robert Ernst, a 59-year old man who allegedly died of a rofecoxib-induced heart attack. The plaintiffs' lead attorney was Mark Lanier. Merck argued that the death was due to cardiac arrhythmia, which had not been shown to be associated with rofecoxib use. The jury awarded Carol Ernst, widow of Robert Ernst, $253.4 million in damages. This award will almost certainly be capped at no more than USD$26.1 million because of punitive damages limits under Texas law. As of March 2006, the plaintiff had yet to ask the court to enter a judgment on the verdict; Merck has stated that it will appeal.

On November 3, 2005, Merck won the second case Humeston v. Merck, a personal injury case, in Atlantic City, New Jersey. The plaintiff experienced a mild myocardial infarction and claimed that rofecoxib was responsible, after having taken it for two months. Merck argued that there was no evidence that rofecoxib was the cause of Humeston's injury and that there

is no scientific evidence linking rofecoxib to cardiac events with short durations of use. The jury ruled that Merck had adequately warned doctors and patients of the drug's risk.

The first federal trial on rofecoxib, Plunkett v. Merck, began on November 29, 2005 in Houston, Texas. The trial ended in a hung jury and a mistrial was declared on December 12, 2005. According to the Wall Street Journal, the jury hung by an eight to one majority, favoring the defense. Upon retrial in February 2006 in New Orleans, Louisiana, where the Vioxx multi-district litigation (MDL) is based, a jury found Merck not liable, even though the plaintiffs had the NEJM editor testify as to his objections to the VIGOR study.

On January 30th, 2006, a New Jersey state court dismissed a case brought by Edgar Lee Boyd, who blamed Vioxx for gastiointestinal bleeding that he experienced after taking the drug. The judge said that Boyd failed to prove the drug caused his stomach pain and internal bleeding.

In January 2006, Garza v. Merck began trial in Rio Grande City, Texas. The plaintiff, a 71-year-old smoker with heart disease, had a fatal heart attack three weeks after finishing a one-week sample of rofecoxib. On April 21, 2006 the jury awarded the plaintiff $7 million compensatory and $25 million punitive. The punitive amount will be reduced to under $1 Million.

On April 5th, the judge overseeing the MDL litigation dismissed Diaz v. Merck on request of the plaintiff. Merck attorney Phil Beck said that the decision of the Plaintiff Steering Council – a group of lawyers coordinating federal cases against Merck -- to not support "Mr. Diaz' case reflects the evidence proving that Mr. Diaz's heart attack was not caused in any way by his use of Vioxx for 19 months." Diaz's attorney said the request was made because there were too many documents to go through, although the trial date had already been delayed twice.

Merck successfully defended in Doherty v Merck where a grandmother claimed that the drug had caused her heart attack. The jury in Atlantic City, New Jersey found that Vioxx did not contribute to her heart attack, that Merck acted responsibly in informing the medical community about the benefits and risks of the drug and that the drug company's marketing efforts did not mislead consumers.

In August 2006, a jury found in favor of Merck in the company's first case in California, Grossberg v. Merck. The jury found that Merck was not negligent, that it did not conceal information and that Vioxx did not cause Grossberg's heart attack.

Merck has reserved $970 million to pay for its Vioxx-related legal expenses through 2007.

Merck sales representatives are now being subpoenaed to court over selling Vioxx to doctors- patients are claiming the reps knew of the side effects and are partially responsible for the wrongful deaths.

Political impact of Vioxx litigation in America

The recall and litigation over rofecoxib has provoked debate over drug safety in the United States. Some argue that the U.S. Food and Drug Administration does not do enough to monitor product safety and that the rofecoxib withdrawal is an argument against tort reform. It has also been argued that litigation is an imperfect means of regulation that would

overdeter companies for complying with FDA requirements, and that large awards like that in Ernst would inhibit research and development.

Other COX-2 inhibitors

It is currently unknown whether the increased risk of adverse cardiovascular events is common to all COX-2 inhibitors. Recent studies have demonstrated the increased risk of cardiovascular events associated with the use of celecoxib (Celebrex), valdecoxib (Bextra) and parecoxib (Dynastat). (Solomon et al., 2005; Nussmeier et al., 2005)

Newer and more specific COX-2 inhibitors, including etoricoxib (Arcoxia) and lumiracoxib (Prexige), are currently (circa 2005) undergoing Phase III/IV clinical trials. It is likely that these trials will be extended in order to supply additional evidence of cardiovascular safety.

A recent systematic review of 114 clinical trials, published in JAMA 2006, evalated the adverse renal (kidney) and arrhythmia risks of celecoxib, valdecoxib, parecoxib, lumiracoxib, and etoricoxib.

Regulatory authorities worldwide now require warnings about cardiovascular risk of COX-2 inhibitors still on the market. For example, in 2005, EU regulators required the following changes to the product information and/or packaging of all COX-2 inhibitors (EMEA 2005):

- Contraindications stating that COX-2 inhibitors must not be used in patients with established ischaemic heart disease and/or cerebrovascular disease (stroke), and also in patients with peripheral arterial disease
- Reinforced warnings to healthcare professionals to exercise caution when prescribing COX-2 inhibitors to patients with risk factors for heart disease, such as hypertension, hyperlipidaemia (high cholesterol levels), diabetes and smoking
- Given the association between cardiovascular risk and exposure to COX-2 inhibitors, doctors are advised to use the lowest effective dose for the shortest possible duration of treatment

Miscellaneous

- Rofecoxib was shown to improve premenstrual acne vulgaris in a placebo controlled study.

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Opioids

An *opioid* is any agent that binds to opioid receptors, found principally in the central nervous system and gastrointestinal tract. There are four broad classes of opioids: endogenous opioid peptides, produced in the body; opium alkaloids, such as morphine (the prototypical opioid) and codeine; semi-synthetic opioids such as heroin and oxycodone; and fully synthetic opioids such as pethidine and methadone that have structures unrelated to the opium alkaloids.

Although the term opiate is often used as a synonym for opioid, it is more properly limited to the natural opium alkaloids and the semi-synthetics derived from them.

Pharmacology

Opioids bind to specific opioid receptors in the central nervous system and in other tissues. There are at least four major classes of opioid receptors: ¼, º, ´ and possibly Ã. In addition, there are two subtypes of ¼ receptor: ¼1 and ¼2.These are all G-protein coupled receptors acting on GABAergic neurotransmission. The pharmacodynamic response to an opioid depends on which receptor it binds, its affinity for that receptor, and whether the opioid is an agonist or an antagonist. For example, the supraspinal analgesic properties of the opioid agonist morphine are mediated by activation of the ¼***1*** receptor, respiratory depression and physical dependence (dependency) by the ¼***2*** receptor, and sedation and spinal analgesia by the º receptor.

Uses

Clinical use

Opioids have long been used to treat acute pain (such as post-operative pain). They have also found to be invaluable in palliative care to alleviate the severe, chronic, disabling pain

of terminal conditions such as cancer. Very high doses are often required in palliation to improve the patients' terminal quality-of-life.

In recent years there has been an increased use of opioids in the management of non-malignant chronic pain. This trend is still somewhat controversial due to issues of dependence.

As recently as the early 20th century, opioids were administered by doctors to treat severe depression and other psychiatric disorders. The practice was discontinued because of the addictive potential of opioids. In recent decades, researchers have experimented with mixed opioid agonist/antagonists such as buprenorphine for the treatment of depression and other psychiatric disorders, encouraged by the decreased liability toward abuse of and dependence on these compounds, compared with full opioid agonists.

United States

The sole clinical indications for opioids in the US, according to Drug Facts and Comparisons, 2005, are

- Analgesia and anesthesia
- Cough (codeine and hydrocodone only)
- Diarrhea (opium only)
- Anxiety due to shortness of breath (oxymorphone only)
- Detoxification (methadone only)

Opioids are prohibited for psychological relief (with the narrow exception of anxiety due to shortness of breath), despite their extensively reported psychological benefits. The basis for this prohibition is not therapeutic but legal (fear of addiction and diversion). The prohibition allows no exceptions, even in areas where researchers have reported opioids to be especially effective and where the possibility of addiction or diversion is very low — for example, in the treatment of senile dementia, geriatric depression, and psychological distress due to chemotherapy or terminal diagnosis.

Recreational use and abuse

Most opioids produce euphoria in many people when ingested orally, intravenously, subcutaneously, rectally, through the nasal membranes, or when smoked. Recreational use and abuse of opioids usually is motivated by a desire to experience this euphoria, which can easily lead to addiction. Tolerance develops rapidly; a regular user may require significantly higher dosages of the drug to achieve the desired effect.

History

Non-clinical use and off-label clinical use were criminalized in the USA by the Harrison Narcotics Tax Act of 1914, and by other laws worldwide. Since then, nearly all non-clinical use and off-label clinical use of opioids has been rated zero on the scale of approval of nearly every social institution. However, in UK the 1926 report of the Departmental Committee on

Morphine and Heroin Addiction under the Chairmanship of the President of the Royal College of Physicians reasserted medical control and established the "British system" of control — which lasted until the 1960s; in the US the Controlled Substances Act of 1970 markedly relaxed the harshness of the Harrison Act.

Before the twentieth century, institutional approval was often higher, even in Europe and America. In some cultures, approval of opioids was significantly higher than approval of alcohol.

Adverse effects

Opioids are associated with a range of adverse drug reactions - mostly associated with their pharmacological actions at opioid receptors.

Common adverse reactions include: nausea and vomiting, drowsiness, dizziness, headache, orthostatic hypotension, itch, dry mouth, miosis, urinary retention, and constipation. (Rossi, 2005)

Infrequent adverse reactions include: dose-related respiratory depression (see below), confusion, hallucinations, delirium, urticaria, hypothermia, bradycardia/tachycardia, ureteric or biliary spasm, muscle rigidity, myoclonus (with high doses), and flushing (due to histamine release, except fentanyl and remifentanil). (Rossi, 2005).

The most serious adverse reaction associated with opioid use is respiratory depression. This can occur with a single dose. Although tolerance develops rapidly, respiratory depression is the mechanism behind the fatal consequences of overdose.

Chronic use of opioids may result in serious constipation, which may progress to bowel obstruction, fecal impaction, or paralytic ileus. Because these conditions may require surgical intervention, stimulant laxatives are generally given as an adjunct to prevent these complications. Physiological tolerance does not develop with regard to constipation. It should be noted that in some therapeutic regimens (such as those aimed at treating diarrhea), mild constipation is a desired effect and hence laxatives would not be given.

With some individuals, opioid use can result in opioid-induced hyperalgesia, whereby individuals using opioids to relieve pain may paradoxically have more pain as a result of their medication. This phenomenon likely results from changes in NMDA receptors in the dorsal horn of the spinal cord.

Both therapeutic and chronic use of opioids can compromise the function of the immune system. Opioids decrease the proliferation of macrophage progenitor cells and lymphocytes, and affect cell differentiation. (Roy & Loh, 1996) Opioids may also inhibit leukocyte migration.

Overdose

Overdose of an opioid can be fatal. The mechanism occurs through depression of the respiratory drive, resulting in hypoxia and eventually death. Opioid overdose can be rapidly reversed with an opioid antagonist such as naloxone or naltrexone. These competitive antagonists bind to the opioid receptors with higher affinity than agonists but do not activate the receptors. This displaces the agonist, attenuating and/or reversing the agonist effects.

However, the elimination half-life of naloxone can be shorter than that of the opioid itself, so repeat dosing or continuous infusion may be required.

Tolerance, Dependence, Addiction, and Abuse

Tolerance is the tendency of the body to adapt to the presence of opioids; this adaptation makes it necessary to use ever-increasing doses of opioids in order to achieve the same effects. Tolerance is more pronounced for some effects than for others.

Dependence is the tendency of the body to manifest a characteristic and unpleasant withdrawal syndrome if regular doses of opioids are abruptly discontinued after tolerance has developed.

Addiction is a psychological attachment to certain effects of opioids (such as the euphoria that many people experience when the drugs are taken in sufficiently large doses) that drives the user to take the drug despite adverse and maladaptive consequences. Dependency and the unpleasantness of withdrawal can work to maintain addiction, although they do not cause it.

All persons receiving opioids for any reason will develop some degree of tolerance and dependence over time, although recent research suggests that these effects can be reduced by the concominant administration of opioid antagonists. [1][2]. Some people will also develop addiction.

Abuse is the misuse or overuse of opioids; the phenomena of tolerance and dependency, combined with the addictive potential presented by some effects of opioids (such as euphoria), make these drugs prime candidates for drug abuse.

Pyschiatric nomenclature in the DSM-IV defines dependence as addiction. As a result, a diagnosis of dependence does not imply that discontinuance of opioids will necessarily trigger a withdrawal syndrome. The nomenclature is being reconsidered for DSM-V.

Tolerance

Tolerance can be detected within 12-24 hours of the administration of morphine (Rang et al., 2003), and similarly for some other opioid agonists. Tolerance results in the necessity for increasing the dose over time to achieve the desired clinical effect.

Tolerance appears to develop first to the analgesic, sedative, emetic, euphoric and respiratory depressive effects of opioids. The miotic and constipating effects are more resistant to the development of tolerance. (Rang et al., 2003)

Dependence and withdrawal issues

Regular use of an opioid for any reason rapidly induces physical dependence, characterized by a highly unpleasant withdrawal syndrome when the drug is discontinued or rapidly reduced in dosage, or when an antagonist is administered, although recent development promises the possibility of chronic opioid use without tolerance or withdrawal[1][2]. The acute withdrawal syndrome generally consists of signs and symptoms opposite to those of the drug when initially administered: severe dysphoria, anxiety, eye

tearing, a runny nose, goose bumps, sweating, nausea, vomiting, cramps and deep pains are common. The speed and severity of withdrawal depends on the half-life of the opioid—heroin withdrawal occurs more quickly and is more severe than methadone withdrawal, but methadone withdrawal takes longer. The acute withdrawal phase is often followed by a protracted phase of depression and insomnia that can last for months.

Physical dependence is distinct from and does not imply psychological addiction, defined as uncontrolled drug use despite harm. However, physical dependence can aggravate psychological addiction when it occurs.

Some patients with narcotic dependence experience recurrent episodes of severe abdominal pain and nausea leading to hospitalizations and extensive diagnostic workups over periods of months to years. The intractable nausea resolves when the pain is treated with narcotics, the patient is able to go home, but another episode recurs when the pain medication runs out.

Withdrawal symptoms can be minimised by slowly tapering the dose over days or weeks, sometimes after switching to a long-acting opioid such as methadone. The symptoms of opioid withdrawal can also be treated with other medications, such as clonidine for sympathetic hyperactivity and a benzodiazepine for anxiety and insomnia.

"Rapid detox" is a relatively new technique that uses opioid antagonists to cause acute withdrawal while the patient is under general anesthesia to eliminate the otherwise extreme discomfort. This procedure has attracted controversy due to its high cost and risk; several patients have died during the procedure. Many pain specialists think that the procedure is unnecessary, and addiction specialists criticize it for doing nothing to keep an addict from relapsing into opioid abuse after the procedure is complete. Indeed, there have been reports of addicts undergoing rapid detox with the full intention of resuming addiction as the technique drastically reduces tolerance thus reducing the cost of addiction. Rapid detox also does not alleviate the protracted withdrawal syndrome that lasts for weeks or months after the acute phase.

Examples of opioids

Endogenous opioids

Opioid-peptides that are produced in the body:

- Endorphins
  - Dynorphins

Enkephalins

Dynorphin Acts through º-opioid receptors, and is widely distributed in the CNS, including in the spinal cord and hypothalamus, including in particular the arcuate nucleus and in both oxytocin and vasopressin neurons in the supraoptic nucleus.

[met]-enkephalin is widely distributed in the CNS;[met]-enkephalin is a product of the proenkephalin gene, and acts through ¼ and ´-opioid receptors.

[leu]-enkephalin , also a product of the proenkephalin gene, acts through ´-opioid receptors

Nociceptin, formerly known as orphanin FQ, is an opioid-related peptide, but it does not act at the classic opioid receptors and actions are not antagonised by the opioid antagonist naloxone. Nociceptin is a potent anti-analgesic. Noiceptin is widely distributed in the CNS; it is found in many regions of the hypothalamus, brainstem, forebrain, as well as in the ventral and dorsal horns of the spinal cord. Nociceptin acts at the NOP1 receptor, formerly known as ORL-1. The receptor is also widely distributed in the brain, including in the cortex, anterior olfactory nucleus, lateral septum, hypothalamus, hippocampus, amygdala, central gray, pontine nuclei, interpeduncular nucleus, substantia nigra, raphe complex, locus coeruleus, and spinal cord.

Endomorphin. Acts through ¼-opioid receptors, and is more potent than other endogenous opioids at these receptors.

²-endorphin is expressed in POMC cells in the arcuate nucleus and in a small population of neurons in the brainstem, and acts through ¼-opioid receptors. ²-endorphin has many effects, including on sexual behavior and appetite.²-endorphin is also secreted into the circulation from pituitary corticotropes and melanotropes. ±-neoendorphin is also expressed in POMC cells in the arcuate nucleus

Opium alkaloids

Phenanthrenes naturally occurring in opium:

- Morphine
- Codeine
- Thebaine

Preparations of mixed opium alkaloids, including papaveretum, are still occasionally used.

Semisynthetic derivatives

- Diacetylmorphine (heroin)
- Oxycodone
- Hydrocodone

Dihydrocodeine
Hydromorphone
Oxymorphone
Nicomorphine

Synthetic opioids

Phenylheptylamines

- Methadone
    - Levo-alphacetylmethadol (LAAM)

Piperanilides

- Fentanyl
    - Alfentanil
    Sufentanil
    Remifentanil
    Ketobemidone
    Carfentanyl
    Ohmefentanyl

Phenylpiperidines

- Pethidine (meperidine)
- Ketobemidone
MPPP
Allylprodine
Prodine
PEPAP

Diphenylpropylamine derivatives

- Propoxyphene
- Dextropropoxyphene
    - Dextromoramide
    Bezitramide
    Piritramide

Benzomorphan derivatives

- Pentazocine
Phenazocine

Oripavine derivatives

- Buprenorphine

Morphinan derivatives

- Butorphanol
Nalbufine
Levorphanol
Levomethorphan

Others

- Dezocine
Etorphine
Lefetamine
Tilidine

- Tramadol

- Loperamide (used for diarrhoea, does not cross the blood-brain barrier)
- Diphenoxylate (used for diarrhoea, does not appreciably cross the blood-brain barrier)

Opioid antagonists

- Naloxone
Naltrexone

See also

- Psychoactive drug

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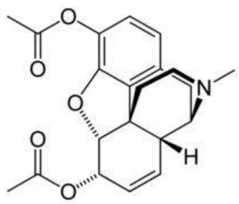
Mu-opioid agonists

Heroin | Morphine

Heroin



Systematic (IUPAC) name

(5±,6±)-7,8-didehydro-4,5-epoxy-
17-methylmorphinan-3,6-diol diacetate (ester)

Identifiers

CAS number 561-27-3

ATC code N02**AA09**

PubChem 3592

Chemical data

Formula $C_{21}H_{23}NO_5$

Mol. weight 369.41

Pharmacokinetic data

Bioavailability <35%

Protein binding 0% (morphine metabolite 35%)

Metabolism hepatic

Half life 2-3 minutes

Excretion 90% renal as glucuronides, rest biliary

Therapeutic considerations

Legal status Schedule I(CA) Class A(UK) Schedule I(US)

Dependence Liability Extremely High

Routes Inhalation, Transmucosal, Intravenous, Oral, Intranasal, Rectal, Intramuscular

Heroin, also known as *diamorphine* (BAN) or *diacetylmorphine* (INN), is a semi-synthetic opioid. It is the 3,6-diacetyl derivative of morphine (hence diacetylmorphine) and is synthesised from it by acetylation. The white crystalline form is commonly the hydrochloride salt, *diacetylmorphine hydrochloride*. It has a high addiction potential, and frequent administration may cause a rapid development of tolerance by the user, especially when compared to other substances, though occasional use may not lead to symptoms of withdrawal.[1][2] Internationally, heroin is controlled under Schedules I and IV of the Single Convention on Narcotic Drugs.[3] It is illegal to manufacture, possess, or sell heroin in the United States; however, under the name *diamorphine*, heroin is a legal prescription drug in the United Kingdom. Popular street names for heroin include gear, diesel, smack, B, skag, Bobby, black tar, horse, junk, jenny, brown, brown sugar, dark, Dope and H.

History

The opium poppy was cultivated in lower Mesopotamia as long ago as 3400 BC.[4] Heroin was first synthesized in 1874 by C.R. Alder Wright, a British chemist working at St. Mary's Hospital Medical School, London. He had been experimenting with combining morphine with various acids. He boiled anhydrous morphine alkaloid with acetic anhydride over a stove for several hours and produced a more potent, acetylated form of morphine, now called diacetylmorphine. The compound was sent to F.M. Pierce of Owens College, Manchester, for analysis, who reported the following to Wright:

Doses ... were subcutaneously injected into young dogs and rabbits ... with the following general results ... great prostration, fear, and sleepiness speedily following the administration, the eyes being sensitive, and pupils dilated, considerable salivation being produced in dogs, and slight tendency to vomiting in some cases, but no actual emesis. Respiration was at first quickened, but subsequently reduced, and the heart's action was diminished, and rendered irregular. Marked want of coordinating power over the muscular movements, and loss of power in the pelvis and hind limbs, together with a diminution of temperature in the rectum of about 4°(rectal failure).[5]

Felix Hoffmann, of Bayer in Elberfeld, Germany, created heroin as a medicine 11 days after inventing aspirin. Afraid of the possible side effects of aspirin, Bayer registered heroin (probably from heroisch, German for heroic, chosen because in field studies people using the medicine felt "heroic") as a trademark.

From 1898 through to 1910 it was marketed as a non-addictive morphine substitute and cough medicine for children. Bayer marketed heroin as a "cure" for morphine addiction before it was discovered that heroin is converted to morphine in the liver. All opiates are converted by the human liver into the identical molecule with varying degrees of concentration in the blood stream. The company felt somewhat embarrassed by this new finding and it became a historical blunder for Bayer.[6] As with aspirin, Bayer lost some of its trademark rights to heroin following World War I.

In the United States in 1914 the Harrison Narcotics Tax Act was passed to control the sale and distribution of heroin. The law still allowed heroin to be prescribed and sold for medical purposes. In particular, addicts could often still be legally supplied with heroin. In 1924, the United States Congress passed additional legislation banning the sale, importation or manufacture of heroin in the United States.

Usage and effects

Indicated for:

Relief of extreme pain
Recreational uses:
Euphoria
Relaxation
Other uses:
Pain relief
Cough suppressant
anti-diarrheal
Contraindications:

Alcohol

Barbiturates and Benzodiazepines

Stimulants

Other opioids (depends heavily on tolerance)

Side effects:

Severe:

Respiratory arrest, seizure, coma, death
Spontaneous abortion
Cardiovascular & Respiratory:
Lowered heart rate
Slowed, shallow or ineffective respiration
Eyes, Ears, nose, and mouth:
Dry mouth
Pupil constriction
Gastrointestinal:
Nausea
Vomiting (protracted)
Constipation
Urinary System:
Urinary retention
Musculoskeletal:

Analgesia

Ataxia
Neurological:

Analgesia

Physical dependence
Psychological:

Anxiolytic

Confusion
Euphoria
Somnolence
Addiction
Skin:
Itching
Flushing/Rash

In the United Kingdom, heroin is available on prescription, though it is a restricted Class A drug. According to the British National Formulary (BNF) edition 50, diamorphine hydrochloride may be used in the treatment of acute pain, myocardial infarction, acute pulmonary edema, and chronic pain. The treatment of chronic non-malignant pain must be supervised by a specialist. The BNF notes that all opioid analgesics cause dependence and tolerance but that this is "no deterrent in the control of pain in terminal illness". When used in the palliative care of cancer patients, heroin is often injected using a syringe driver. In comparison to morphine, it may cause less nausea, hypotension, but more sedation and euphoria and can be dissolved in a smaller quantity of liquid.

Heroin is also widely and illegally used as a powerful and addictive drug that produces intense euphoria, which often disappears with increasing tolerance. It is thought that heroin's popularity with recreational users, compared to morphine or other opiates, comes from its somewhat different perceived effects.[7] This in turn comes from its high lipid solubility provided by the two acetyl groups, resulting in a very rapid penetration of the blood-brain barrier after use. Heroin can be taken or administered in a number of ways, including snorting and injection. It may also be smoked by inhaling the vapors produced when heated from below (known as "chasing the dragon").

Many users in the United Kingdom dissolve the drug together with crack cocaine in a so-called "speedball" or "snowball", which is injected intravenously. This causes an even more intense rush but is more dangerous than heroin alone because the mixture of short-acting stimulant with longer-acting depressant increases the risk of overdosing on one or both drugs. Cocaine is an irritant to all bodily tissues causing eventual necrosis at any site with which it is in frequent contact. Because crack must be acidified with extra citric acid or vitamin C to allow it to dissolve in water, worse vein damage may result than from injecting heroin alone.

Once in the brain, heroin is rapidly metabolized into morphine by removal of the acetyl groups. It is the morphine molecule that then binds with opioid receptors and produces the subjective effects of the heroin high. Heroin is therefore a prodrug.

The onset of heroin's effects is dependent on the method of administration. Orally, the heroin is totally metabolized in vivo into morphine before crossing the blood-brain barrier, so the effects are the same as morphine when taken by mouth. Snorting heroin results in

onset within 10 to 15 minutes. Smoking heroin results in an almost immediate, though mild effect which strengthens the longer it is used in that particular session. Intravenous injection results in rush and euphoria within 7 to 8 seconds, while intramuscular injection takes longer, having an effect within 5 to 8 minutes.

Heroin is a ¼-opioid (mu-opioid) agonist. It acts on endogenous ¼-opioid receptors that are spread in discrete packets throughout the brain, spinal cord and gut in almost all mammals. Heroin, along with other opioids, are agonists to four endogenous neurotransmitters. They are ^{2}-endorphin, dynorphin, leu-enkephalin, and met-enkephalin. The body responds to heroin in the brain by reducing (and sometimes stopping) production of the endogenous opioids when heroin is present. Endorphins are regularly released in the brain and nerves and attenuate pain. Their other functions are still obscure, but are probably related to the effects produced by heroin besides analgesia (antitussin, anti-diarrheal). The reduced endorphin production in heroin users creates a dependence on the heroin, and the cessation of heroin results in extremely uncomfortable symptoms including pain (even in the absence of physical trauma). This set of symptoms is called withdrawal syndrome. It has an onset 6 to 8 hours after the last dose of heroin.

Production and trafficking

Manufacturing

Heroin is produced for the black market through opium refinement processes. Unlike drugs such as LSD, the production of which requires considerable expertise in chemistry and access to constituents which are now tightly controlled, the refinement of the first three grades of heroin from opium is a relatively simple process requiring only moderate technical expertise and common chemicals. The final grade of heroin favored in the west is more difficult to produce and involves a potentially dangerous chemical procedure.

First, morphine is isolated from crude opium by being dissolved in water, reacted with lime fertilizer such that it (morphine) precipitates out, and then reacted again with ammonia. What remains is then mechanically filtered to yield a final product of morphine weighing about 90% less than the original quantity of opium. The morphine is reacted with acetic anhydride — a chemical also used in the production of aspirin — in the complicated five-step process used by most refineries in the Golden Triangle. The first step is to cook the morphine at 85°C (185°F) for six hours with an equivalent weight of acetic anhydride. In the second, a treatment of water and hydrochloric acid then purifies the product moderately. When the chemists add sodium carbonate, the particulates settle. Step four involves heating the heroin in a mixture of alcohol and activated charcoal until the alcohol evaporates. The fifth step is optional, as it only changes the heroin into a finer white powder, more easily injectable; this so-called "no. 4 heroin" is principally exported to the Western markets. In this last, most dangerous step, the heroin (after being dissolved in alcohol), precipitates out in tiny white flakes when a mixture of ether and hydrochloric acid is injected; this step is dangerous due to the fact that the ether may explode, leveling or severely damaging the refinery (as has happened to a number of such facilities).

The purity of the extracted morphine determines in large part the quality of the resulting heroin. Most black market heroin is highly impure due to contaminants left after refinement of opium into morphine which then remain in the final product; even if the final product is in the upper range of purity (80–99% pure), once it reaches the consumer, it typically has been cut multiple times.

History of heroin traffic

The origins of the present international illegal heroin trade can be traced back to laws passed in many countries in the early 1900s that closely regulated the production and sale of opium and its derivatives including heroin. At first, heroin flowed from countries where it was still legal into countries where it was no longer legal. By the mid-1920s, heroin production had been made illegal in many parts of the world. An illegal trade developed at that time between heroin labs in China (mostly in Shanghai and Tientsin) and other nations. The weakness of government in China and conditions of civil war enabled heroin production to take root there. Chinese triad gangs eventually came to play a major role in the heroin trade.

Heroin trafficking was virtually eliminated in the U.S. during World War II due to temporary trade disruptions caused by the war. Japan's war with China had cut the normal distribution routes for heroin and the war had generally disrupted the movement of opium. After the second world war, the Mafia took advantage of the weakness of the postwar Italian government and set up heroin labs in Sicily. The Mafia took advantage of Sicily's location along the historic route opium took from Iran westward into Europe and the United States. Large scale international heroin production effectively ended in China with the victory of the communists in the civil war in the late 1940s. The elimination of Chinese production happened at the same time that Sicily's role in the trade developed.

Although it remained legal in some countries until after World War II, health risks, addiction, and widespread abuse led most western countries to declare heroin a controlled substance by the latter half of the 20th century.

Between the end of World War II and the 1970s, much of the opium consumed in the west was grown in Iran, but in the late 1960s, under pressure from the U.S. and the United Nations, Iran engaged in anti-opium policies. While opium production never ended in Iran, the decline in production in those countries led to the development of a major new cultivation base in the so-called "Golden Triangle" region in South East Asia. In 1970-71, high-grade heroin laboratories opened in the Golden Triangle. This changed the dynamics of the heroin trade by expanding and decentralizing the trade. Opium production also increased in Afghanistan due to the efforts of Turkey and Iran to reduce production in their respective countries. Lebanon, a traditional opium supplier, also increased its role in the trade during years of civil war.

After the overthrow of the Shah of Iran, the new Iranian regime was much more tolerant of opium production. At the same time, the Soviet-Afghan war led to increased production in the Pakistani-Afghani border regions. Both events led to increased international production of heroin at lower prices in the 1980s. The trade shifted away from Sicily in the late 1970s as various criminal organizations violently fought with each other over the trade. The

fighting also led to a stepped up government law enforcement presence in Sicily. All of this combined to greatly diminish the role of the country in the international heroin trade.

Dr Alfred W. McCoy's account of the history of the heroin trade

Although it was beginning to become more prevalent by the 1930s, Asian historian and drug traffic expert Dr Alfred W. McCoy reports that heroin trafficking was virtually eliminated in the U.S. during World War II due to temporary trade disruptions caused by the war. McCoy contends the Mafia was able to gain control of the heroin trade thanks in large measure due to the unintended consequences of a covert deal between top Mafia leader Lucky Luciano and American military intelligence. The deal resulted in a large increase in Mafia influence in Sicily after the 1943 American invasion.

In southeast Asia, the governments of most countries and many colonial officials had been involved in the opium trade for a very long time. Thanks to Corsican Mafia connections in the former French colony of Vietnam, Luciano was able to begin to develop Southeast Asia as a new source of Opium even as Iranian production declined. The Vietnam War and CIA operations in Laos had the unintended consequence of first opening up many areas of Southeast Asia to modern transportation and then presenting a ready-made market for the drug among the U.S. military personnel stationed in the region.

The turning point came in 1970-71 when the first high-grade heroin laboratories opened in the Golden Triangle. Prior to this, the chemical skills for refinement had existed only in Europe. This gave the opium producers control over the creation of the final product. The hundreds of thousands of American servicemen in Vietnam provided a perfect market for the heroin producers, and heroin use among soldiers rapidly increased. In 1971 the first large consignments of South East Asian heroin were intercepted in Europe and America, and by the mid-1970s heroin addiction fulfilled its promise as a serious social problem in the United States, Australia, the United Kingdom, and many other nations.

Trafficking

See also: Opium production

Traffic is heavy worldwide, with the biggest producer being Afghanistan. [8] According to U.N. sponsored survey,[9] as of 2004, Afghanistan accounted for production of 87 percent of the world's heroin.[10] Opium production in that country has increased rapidly since, reaching an all-time high in 2006. War once again appeared as a facilitator of the trade.[11]

Dr. Alfred W. McCoy has claimed that the C.I.A. secretly collaborated with Asian drug syndicates and was complicit in the expansion of the global heroin trade from 1970 to 1973 in order to prosecute the Cold War. While the Vietnam War brought modern transportation to remote opium areas, McCoy himself does not claim that the CIA set up the drug labs in Southeast Asia or created the trade.

Heroin is one of the most profitable illicit drugs since it is compact and easily concealed. At present, opium poppies are mostly grown in the Middle East, Pakistan, and Afghanistan, and in Asia, especially in the region known as the Golden Triangle straddling Myanmar,

Thailand, Vietnam, Laos and Yunnan province in the People's Republic of China. There is also cultivation of opium poppies in the Sinaloa region of Mexico and in Colombia. The majority of the heroin consumed in the United States comes from Mexico and Colombia. Up until 2004, Pakistan was considered one of the biggest opium-growing countries. However, the efforts of Pakistan's Anti-Narcotics Force have since reduced the opium growing area by 59% as of 2001. Some suggest that the decline in Pakistani production is inversely proportional to the rise of Afghani production, and that rather than anti-narcotics activity, the decline in Pakistan is due more to changed market forces.

Conviction for trafficking in heroin carries the death penalty in most Southeast Asia and some East Asia, southern Asia and Middle East countries (see Use of death penalty worldwide for details), among which Malaysia, Singapore and Thailand are the most strict. The penalty applies even to citizens of countries where the penalty is not in place, sometimes causing controversy when foreign visitors are arrested for trafficking, for example the arrest of nine Australians in Bali or the hanging of Australian citizen Van Tuong Nguyen in Singapore, both in 2005.

Risks of non-medical use

- Overdose, possibly causing death

For intravenous users of heroin, the use of non-sterile needles and syringes and other related equipment leads to the risk of contracting blood-borne pathogens such as HIV and hepatitis, as well as the risk of contracting bacterial or fungal endocarditis and possibly Venous sclerosis

Poisoning from contaminants added to "cut" or dilute heroin

Chronic constipation

Heroin-induced leukoencephalopathy (very rare, smokers only)

Many countries and local governments have begun funding programs that supply sterile needles to people who inject illegal drugs in an attempt to reduce these contingent risks and especially the contraction and spread of blood-borne diseases. The Drug Policy Alliance reports that up to 75% of new AIDS cases among women and children are directly or indirectly a consequence of drug use by injection. But despite the immediate public health benefit of needle exchanges, some see such programs as tacit acceptance of illicit drug use. The United States does not support needle exchanges federally by law, and although some state and local governments do support needle exchange programs, they continue to face harassment by police in most areas. Needle exchanges have been instrumental in arresting the spread of HIV/AIDS in many communities with a significant heroin using population, Australia being a leader due to its early inception of needle exchanges. Needle exchange programs have also been attributed to saving the public significant amounts of tax dollars by preventing medical costs which would have been required otherwise for the treatment of diseases spread through the practice of sharing and reusing needles.

A heroin overdose is usually treated with an opioid antagonist, such as naloxone (Narcan) or naltrexone, which have a high affinity for opioid receptors but do not activate them. This blocks heroin and other opioid agonists and causes an immediate return of consciousness and the beginning of withdrawal symptoms when administered intravenously. The half-life of these antagonists is usually much shorter than that of the opiate drugs they are used to

block, so the antagonist usually has to be re-administered multiple times until the opiate has been metabolized by the body.

Depending on drug interactions and numerous other factors, death from overdose can take anywhere from several seconds to several hours. An overdose is immediately reversible with an opioid antagonist injection. Heroin overdoses can occur due to an unexpected increase in the dose or purity or due to diminished opiate tolerance. However, many fatalities reported as overdoses are probably caused by interactions with other depressant drugs like alcohol or benzodiazepines.[12]

The LD***50*** for a person already addicted is prohibitively high, to the point that there is no general medical consensus on where to place it. Several studies done in the 1920s gave addicts doses of 1,600–1,800 mg of heroin in one sitting, and no adverse effects were reported. This is approximately 160–180 times a normal recreational dose. Even for a non-addict, the LD***50*** can be credibly placed above 350 mg.

Street heroin is of widely varying and unpredictable purity. This means that an addict may prepare what they consider to be a moderate dose while actually taking far more than intended. Also, relapsing addicts after a period of abstinence have tolerances below what they were during active addiction. If a dose comparable to their previous use is taken an overdose often results.

A final source of overdose in addicts comes from place conditioning. Heroin use, like other drug abuse behaviors, is highly ritualized. While the mechanism has yet to be clearly elucidated, it has been shown that longtime heroin users, immediately before injecting in a common area for heroin use, show an acute increase in metabolism and a surge in the concentration of opiate-metabolizing enzymes. This acute increase, a reaction to a location where the addict has repeatedly injected heroin, imbues the addict with a strong (but temporary) tolerance to the toxic effects of the drug. When the addict injects in a different location, this place-conditioned tolerance does not occur, giving the addict a much lower-than-expected ability to metabolize the drug. The user's typical dose of the drug, in the face of decreased tolerance, becomes far too high and can be toxic, leading to overdose.[1]

A small percentage of heroin smokers may develop symptoms of leukoencephalopathy. This is believed to be caused by an uncommon adulterant that is only active when heated. Symptoms include slurred speech and difficulty walking. Contrary to popular rumor, aluminum foil probably has nothing to do with the development of leukoencephalopathy in heroin users.

Withdrawal

The withdrawal syndrome from heroin may begin starting from within 6 to 24 hours of discontinuation of sustained use of the drug; however, this time frame can fluctuate with the degree of tolerance as well as the amount of the last consumed dose. Symptoms may include: sweating, malaise, anxiety, depression, persistent and intense penile erection in males (priapism), extra sensitivity of the genitals in females, general feeling of heaviness, cramp-like pains in the limbs, yawning and lacrimation, sleep difficulties, cold sweats, chills, severe muscle and bone aches not precipitated by any physical trauma, nausea and vomiting, diarrhea, goose bumps, cramps, and fever. Many addicts also complain of a painful condition, the so-called "itchy blood", which often results in compulsive scratching that causes bruises

and sometimes ruptures the skin leaving scabs. Abrupt termination of heroin use causes muscle spasms in the legs of the user (restless leg syndrome). Users taking the "cold turkey" approach (withdrawal without using symptom-reducing or counteractive drugs) are more likely to experience the negative effects of withdrawal in a more pronounced manner.

Two general approaches are available to facilitate the physical part of opioid withdrawal. The first is to substitute a longer-acting opioid such as methadone or buprenorphine for heroin or another short-acting opioid and then slowly taper the dose.

In the second approach, benzodiazepines such as diazepam (Valium) may temporarily ease the often extreme anxiety of opioid withdrawal. The most common benzodiazepine employed as part of the detox protocol in these situations is oxazepam (Serax). Benzodiazepine use must be prescribed with care because benzodiazepines have a great addiction potential, and many opioid addicts also use other central nervous system depressants including benzodiazepines and sometimes even the obsolete barbiturates. Also, though unpleasant, opioid withdrawal seldom has the potential to be fatal, whereas complications related to withdrawal from benzodiazepines, barbiturates and alcohol (such as epileptic seizures, cardiac arrest, and delirium tremens) can prove hazardous and potentially fatal. Many symptoms of opioid withdrawal are due to rebound hyperactivity of the sympathetic nervous system, which can be suppressed with clonidine (Catapres), a centrally-acting alpha-2 agonist primarily used to treat hypertension.

Buprenorphine is one of the substances most recently licensed for the substitution of illegal opioids. Being a partial opioid agonist/antagonist, it develops a lower grade of tolerance than heroin or methadone due to the so-called ceiling effect. It also has less severe withdrawal symptoms than heroin when discontinued abruptly, which should never be done without proper medical supervision. It is usually administered every 24-48 hrs. Buprenorphine is a kappa-opioid receptor antagonist. This gives the drug an anti-depressant effect, increasing physical and intellectual activity. Buprenorphine also acts as a partial agonist at the same ¼-receptor where illicit opioids like heroin exhibit their action. Due to its effects on this receptor, all patients whose tolerance is above a certain level are unable to obtain any "high" from other opioids during buprenorphine treatment except for very high doses.

Researchers at Johns Hopkins University have been testing a sustained-release "depot" form of buprenorphine that can relieve cravings and withdrawal symptoms for up to six weeks.[13] A sustained-release formulation would allow for easier administration and adherence to treatment, and reduce the risk of diversion or misuse.

Methadone is another ¼-opioid agonist most often used to substitute for heroin in treatment for heroin addiction. Compared to heroin, methadone is well (but slowly) absorbed by the gastrointestinal tract and has a much longer duration of action of approximately 24 hours. Thus methadone maintenance avoids the rapid cycling between intoxication and withdrawal associated with heroin addiction. In this way, methadone has shown some success as a "less harmful substitute"; despite bearing about the same addiction potential as heroin, it is recommended for those who have repeatedly failed to complete withdrawal or have recently relapsed. As of 2005, the ¼-opioid agonist buprenorphine is also being used to manage heroin addiction, being a superior, though still imperfect and not yet widely known alternative to methadone. Methadone, since it is longer-acting, produces withdrawal symptoms that appear later than with heroin, but usually last considerably

longer and can in some cases be more intense. Methadone withdrawal symptoms can potentially persist for over a month, compared to heroin where significant physical symptoms would subside by 4 days.

Two opioid antagonists are known: naloxone and the longer-acting naltrexone. These two medications block the effects of heroin, as well as the other opioids at the receptor site. Recent studies have suggested that the addition of naloxone and naltrexone may improve the success rate in treatment programs when combined with the traditional therapy.

The University of Chicago undertook preliminary development of a heroin vaccine in monkeys during the 1970s, but it was abandoned. There were two main reasons for this. Firstly, when immunised monkeys had an increase in dose of x16, their antibodies became saturated and the monkey had the same effect from heroin as non-immunised monkeys. Secondly, until they reached the x16 point immunised monkeys would substitute other drugs to get a heroin-like effect. These factors suggested that immunised human addicts would simply either take massive quantities of heroin, or switch to other hard drugs, which is known as cross-tolerance.

There is also a controversial treatment for heroin addiction based on a plant-derived African psychedelic drug, ibogaine. Many people travel abroad for ibogaine treatments that generally interrupt the addiction for 3 - 6 months or more in up to 80% of patients. Relapse often occurs when the person returns home to their normal environment however, where drug seeking behaviour may return in response to social and environmental cues. Ibogaine treatments are carried out in several countries in South America and in Europe but can be dangerous. Some addicts find the ibogaine therapy most effective when it is given several times over the course of a few months or years, but this can be very expensive. A synthetic derivative of ibogaine, 18-methoxycoronaridine is in phase 2 trials in humans as an anti-addictive drug.

Heroin prescription

In 1994 Switzerland began a trial program featuring a heroin prescription for addicts not well suited for withdrawal programs—e.g. those that had failed multiple withdrawal programs. The aim is maintaining the health of the addict in order to avoid medical problems stemming from low-quality street heroin. Reducing drug-related crime was another goal. Addicts can more easily get or maintain a paid job through the program as well. The first trial in 1994 began with 340 addicts and it was later expanded to 1000 after medical and social studies suggested its continuation. Participants are prescribed to inject heroin in specially designed pharmacies for about US $13 per dose.[14]

The success of the Swiss trials led German, Dutch,[15] and Canadian[16] cities to trial their own heroin prescription programs.[17] Some Australian cities (such as Sydney) have trialed legal heroin injecting rooms, in line with other wider harm minimisation programs. Heroin is unavailable on prescription however, and remains illegal outside the injecting room, and effectively decriminilised inside of the injecting room. [citation needed]

Drug interactions

Opioids are strong central nervous system depressants, but regular users develop physiological tolerance allowing gradually increased dosages. In combination with other central nervous system depressants, heroin may still kill even experienced users, particularly if their tolerance to the drug has reduced or the strength of their usual dose has increased.

Toxicology studies of heroin-related deaths reveal frequent involvement of other central nervous system depressants, including alcohol, benzodiazepines such as diazepam (valium), and, to a rising degree, methadone. Ironically, benzodiazepines are often used in the treatment of heroin addiction while they cause much more severe withdrawal symptomes.

Cocaine also proves to be often fatal when used in combination with heroin. Though "speedballs" (when injected) or "moonrocks" (when smoked) are a popular mix of the two drugs among users, combinations of stimulants and depressants can have unpredictable and sometimes fatal results. In the United States in early 2006, a rash of deaths was attributed to either a combination of fentanyl and heroin, or pure fentanyl masquerading as heroin particularly in the Detroit Metro Area; one news report refers to the combination as 'laced heroin', though this is likely a generic rather than a specific term.[18]

Culture

Heroin has inspired countless writers, musicians and other artists over the past century of use. However, its influence is often misunderstood or unfairly assumed; many creative people have used or been addicted to heroin, but the extent to which the drug affected their creativity is debatable. Relatively few artists with great talent have credited heroin use with major epiphanies.

See also

- Hillbilly heroin
- Morphine
- Psychoactive drug
- Opium

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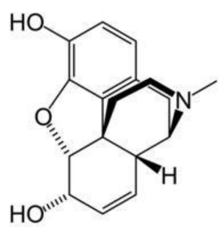
- Heroin: A True Story of Addiction, Hope and Triumph by Julie O'Toole (paperback 2005) ISBN 1-905-37901-3

Morphine



Systematic (IUPAC) name

7,8-didehydro-
4,5-epoxy-17-methylmorphinan-3,6-diol

Identifiers

CAS number 57-27-2

ATC code N02**AA01**

PubChem 5288826

DrugBank APRD00215

Chemical data

Formula $C_{17}H_{19}NO_3$

Mol. weight 285.4

Pharmacokinetic data

Bioavailability **~30%**

Protein binding 30–40%

Metabolism Hepatic 90%

Half life 2–3 hours

Excretion Renal 90%, biliary 10%

Therapeutic considerations

Pregnancy cat. $C_{(AU)}$ $C_{(US)}$

Legal status S8(AU) Schedule I(CA) Class A(UK) Schedule II(US) Prescription only

Dependence Liability Extremely High

Routes smoked/inhaled, insufflated, Oral, SC, IM, IV

Morphine (INN) (IPA: [ÈmT(y)fin]) is an extremely powerful opiate analgesic drug and is the principal active agent in opium. Like other opioids, e.g. heroin, morphine acts directly on the central nervous system (CNS) to relieve pain, and at synapses of the arcuate nucleus, in particular. Side effects include impairment of mental performance, euphoria, drowsiness, lethargy, and blurred vision. It also decreases hunger, inhibits the cough reflex, and produces constipation. Morphine is highly addictive when compared to other substances, and tolerance and physical and psychological dependence develop quickly. Patients on morphine often report insomnia, visual hallucinations and nightmares. Used in ACS "Chest Pain believed to be of cardiac origin" as an adjunct to nitroglycerine providing pain relief, decreasing patient anxiety and minimal coronary artery dilation, which helps oxygenate the heart.

The word "morphine" is derived from Morpheus, the god of dreams in Greek mythology. He is the son of Somnus, god of sleep.

Medical use

Administration

Parenterally as subcutaneous, intravenous, or epidural injections. When injected, particularly intravenously, morphine produces an intense contraction sensation in the muscles and thus produces a powerful 'rush'. The military sometimes issues morphine loaded in an autoinjector.

Orally, it comes as an elixir, concentrated solution, powder (for compounding) or in tablet form. Morphine is rarely supplied in suppository form. Due to its poor oral bioavailability, oral morphine is only one-sixth to one-third of the potency of parenteral morphine. Morphine is available in extended-release capsules for chronic administration, as well as immediate-release formulations.

Uses

Morphine is used legally:

- analgesic in hospital settings for
  - Pain after surgery
  - Pain associated with trauma
- In the relief of severe chronic pain
  - Cancer pain
  - Pain from kidney stones
  - Back pain
- As an adjunct to general anesthesia
- In epidural anesthesia
- For palliative care (i.e. to alleviate pain without curing the underlying reason for it)
- As an antitussive for severe cough
- As an antidiarrheal in chronic conditions (e.g., for diarrhea associated with AIDS)

Contraindications

- acute respiratory depression

acute alcoholism
acute pancreatitis (this may be a result of morphine use as well)
renal failure (due to accumulation of the metabolite morphine-6-glucuronide)

Pharmacology

Indicated for:

Relief of extreme pain

Recreational uses:
Euphoria
Relaxation
Other uses:
Pain relief
Cough suppressant
anti-diarrheal
Contraindications:

Alcohol

Barbiturates and Benzodiazepines

Stimulants

Other opioids (depends heavily on tolerance)

Side effects:

Severe:

Respiratory arrest
Spontaneous abortion
Cardiovascular:
Lowered heart rate
Ear, nose, and throat:
Dry mouth
Endocrinal:
Eugonadism
Eye:
Pupil constriction
Intermittent blurring
Gastrointestinal:
Nausea
Constipation
Hepatological:

- none

Neurological:

Analgesia

Psychological:

Anxiolysis

Confusion
Euphoria
Sedation
Respiratory:
Slow and shallow respiration
Skin:
Itchiness
Flushing

Morphine is an phenanthrene opioid receptor agonist – its main effect is binding to and activating the μ-opioid receptors in the central nervous system. Activation of these receptors is associated with analgesia, sedation, euphoria, physical dependence and respiratory depression. Morphine is also a º-opioid receptor agonist, with this action associated with spinal analgesia and miosis.

Like loperamide and other opioids, morphine acts on the myenteric plexus in the intestinal tract reduce gut motility, leading to constipation.

The effects of morphine can be countered with naloxone or naltrexone.

Morphine is primarily metabolized into morphine-3-glucuronide and morphine-6-glucuronide. Morphine-6-glucuronide (M6G) has been found to be a far more potent analgesic than morphine when dosed to rodents. M6G has also been found to be analgesic in humans. The significance of M6G formation on the observed effect of a dose of morphine is the subject of extensive debate among pharmacologists.

High doses of morphine may be fatal due to respiratory depression. Nevertheless, patients in extreme pain are able to tolerate very high doses of morphine. This is because pain stimulates respiration, thus counteracting the respiratory depression.

Legal classification

- In the United Kingdom, morphine is listed as a Class A drug under the Misuse of Drugs Act 1971.
- In the United States, morphine is classified as a Schedule II drug under the Controlled Substances Act.
- In Australia, morphine is classified as a Schedule 8 drug under the Therapeutic Goods Act 1989 (2003).[1]
- Internationally, morphine is a Schedule I drug under the Single Convention on Narcotic Drugs[2].

History and abuse

Morphine was first isolated in 1804 by the German pharmacist Friedrich Wilhelm Adam Sertürner (or Barnard Courtois), who named it "morphium" after Morpheus, the Greek god of dreams. But it was not until the development of the hypodermic needle (1853) that its use spread. It was used for pain relief, and as a "cure" for opium and alcohol addiction. Its extensive use during the American Civil War allegedly resulted in over 400,000 sufferers from the "soldier's disease" of morphine addiction, although critics believe this to be a highly

erroneous and misleading claim, pointing to the glaring lack of documented post-war cases[3].

Heroin (diacetylmorphine) was derived from morphine in 1874. As with other drugs, its possession without a prescription was criminalized in the U.S. by the Harrison Narcotics Tax Act of 1914.

Morphine is routinely carried by soldiers on operations in an autoinjector.

Morphine was the most commonly abused narcotic analgesic in the world up until heroin was synthesized and came into use. Even today, morphine is one of the most sought after prescription narcotics by heroin addicts when heroin is scarce.

In a randomised double-blind study with crossover at an outpatient clinic in Bern, Switzerland, morphine was proven to have stronger side-effects than heroin at equianalgesic doses. Respiratory depression, miosis, sedation, itchiness, and euphoria were more pronounced with morphine.

See also

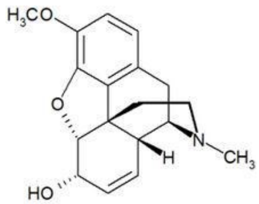
- Heroin
- Opium
- Psychoactive drug

Natural opium alkaloids

The term *opiate* refers to the alkaloids found in opium, an extract from the seed pods of the opium poppy (Papaver somniferum L.). It has also traditionally referred to natural and semi-synthetic derivatives of morphine. The term is often incorrectly used to refer to all drugs with opium- or morphine-like pharmacological action, which are more properly classified under the broader term opioid.

The main opiates derived from opium are morphine, codeine and thebaine. Papaverine and noscapine are also present, but have essentially no effect on the central nervous system, and are not usually considered to be opioids. Papaveretum is a standardised preparation of mixed opium alkaloids used on cardiac patients.

Codeine



Systematic (IUPAC) name

7,8-didehydro-4,5-epoxy-3-methoxy-17-methylmorphinan-6-ol

Identifiers

CAS number 76-57-3

ATC code R05**DA04**

PubChem 5284371

DrugBank APRD00120

Chemical data

Formula $C_{18}H_{21}NO_{3}$

Mol. weight 299.364 g/mol

Pharmacokinetic data

Bioavailability **well absorbed**

Metabolism Hepatic

Half life 2–4 hours

Excretion renal

Therapeutic considerations

Pregnancy cat. A(AU)

Legal status S8(AU) Schedule I(CA) Class B(UK) Schedule II(US)

Routes oral, intra-nasally, intra-rectally, SC, IM

Codeine (INN) or *methylmorphine* is an opiate used for its analgesic, antitussive and antidiarrheal properties. It is marketed as the salts *codeine sulfate* and *codeine phosphate*. *Codeine hydrochloride* is more commonly marketed in continental Europe and other regions.

Codeine is an alkaloid found in opium in concentrations ranging from 0.3 to 3.0 percent. While codeine can be extracted from opium, most codeine is synthesized from morphine through the process of O-methylation.

Indications

Approved indications for codeine include:

- Cough, though its efficacy has been disputed.[1]
- Diarrhea
- Moderate to severe pain

Codeine is sometimes marketed in combination preparations with paracetamol (acetaminophen) as co-codamol (best known as Tylenol 3), with aspirin co-codaprin or with ibuprofen. These combinations provide greater pain relief than either agent used alone (q.v. Drug Synergy).

Controlled substance

In the United States, codeine is regulated by the Controlled Substances Act. It is a Schedule II controlled substance for pain-relief products containing codeine alone. In combination with aspirin or acetaminophen (paracetamol/tylenol) it is listed as Schedule III. Codeine is also available outside the United States as an over-the-counter drug in liquid cough-relief formulations. Internationally, codeine is a Schedule II drug under the Single Convention on Narcotic Drugs.[2]

In the United Kingdom, codeine is regulated by the Misuse of Drugs Act 1971; it is a Class B drug, except for concentrations of less than 8 mg when combined with paracetamol, or 12.5 mg when combined with ibuprofen, which are available in many over the counter preparations.

In Australia, New Zealand and Canada, codeine is regulated; however, it is available without prescription in combination preparations from licensed pharmacists in doses up to 15 mg/tablet (8 mg/tablet in Canada).

In Canada, codeine can only be sold in combination with 2 or more ingredients, which has resulted in the prevalence of AC&C (aspirin, codeine, and caffeine), and similar combinations using acetaminophen rather than asprin. Caffeine, being a stimulant, tends to offset the sedative effects of codeine.

Pharmacokinetics

Codeine is considered a prodrug, since it is metabolised in vivo to the principal active analgesic agent morphine. It is, however, less potent than morphine since only about 10% of the codeine is converted. It also has a correspondingly lower dependence-liability than morphine.

Theoretically, a dose of approximately 200 mg (oral) of codeine must be administered to give equivalent analgesia to 30 mg (oral) of morphine (Rossi, 2004). It is not used, however, in single doses of greater than 60mg (and no more than 240 mg in 24 hours) since there is a ceiling effect.

The conversion of codeine to morphine occurs in the liver and is catalysed by the cytochrome P450 enzyme CYP2D6. Approximately 6–10% of the Caucasian population have poorly functional CYP2D6 and codeine is virtually ineffective for analgesia in these patients (Rossi, 2004). Many of the adverse effects, however, are still experienced. Also, some medications are CYP2D6 inhibitors and reduce or even completely eliminate the efficacy of codeine. The most notorious of these are the selective serotonin reuptake inhibitors, such as fluoxetine (Prozac) and citalopram (Celexa).

Pharmacology

Codeine itself has weak affinity for the ¼-opioid receptor. Its principal analgesic actions are mediated by the affinity of morphine for the ¼-opioid receptor, though other therapeutic and adverse effects are produced by activation of other opioid receptors.

Adverse effects

Common adverse drug reactions associated with the use of codeine include itching, nausea, vomiting, drowsiness, dry mouth, miosis, orthostatic hypotension, urinary retention and constipation.[3]

Tolerance to many of the effects of codeine develops with prolonged use, including therapeutic effects. The rate at which this occurs develops at different rates for different effects, with tolerance to the constipation-inducing effects developing particularly slowly for instance.

A potentially serious adverse drug reaction, as with other opioids, is respiratory depression. This depression is dose-related and is the mechanism for the potentially fatal consequences of overdose.

Another side effect commonly noticed is the lack of sexual drive. It is generally due to lethargy caused by abuse of codeine.

Codeine has also been known to interact negatively with some psychiatric medications such as reboxetine and venlafaxine.

Recreational use

Codeine is often used as a recreational drug. This may be due to its easy availability over the counter or on prescription in combination products (which, in certain countries, are scheduled lower than codeine as a single-agent). People use it in order to obtain the euphoric effects associated with use of opioids. Codeine-containing cough syrups are often taken whole by drinking the syrup; combination pills may be taken whole or crushed and insufflated (snorted), or the codeine may be extracted using methods like cold water extraction.

- In certain areas of the United States, such as Texas, codeine in syrup form is called Lean. It is commonly mixed with alcohol, or into a joint (marijuana cigarette) and smoked.
- When prepared with promethazine, codeine is a Schedule V controlled substance in the United States. In a few states, such as New Jersey, codeine with promethazine is available over the counter. The syrup, sometimes known as Phenergan With Codeine, contains 6.25 mg of promethazine and 10 mg of codeine per teaspoonful.
- In some countries, cough syrups and tablets containing codeine are available without prescription; people will frequently purchase it from multiple pharmacies so as not to incur suspicion. It is reported that in France, 95% of the consumption of Néo-codion cough preparation, containing codeine, cannot be attributed to medical use, but is rather used as a substitute for heroin. A heroin addict may use codeine to ward off the effects of a withdrawal.[4]
- In the United Kingdom, people purchase tablets which combine codeine and paracetamol (acetaminophen), and consume these at higher-than-recommended doses, without apparent concern of the hepatotoxicity associated with large doses of paracetamol. Some try to extract the codeine from the

paracetamol through various methods, the most common and simplest being the cold water extraction.

- While the combination of codeine with paracetamol at higher-than-recommended doses can possibly cause hepatotoxicity (liver damage), combination with ibuprofen can result in kidney problems/failure and additional stomach pain and nausea, and combination with aspirin can lead to internal hemorrhaging, particularly gastrointestinal hemorrhage.
- In South Asian countries codeine has become a multi-million-dollar market in the form of codeine-phosphate-containing cough syrups which are easily available at chemist shops without a prescription, notable among them being Corex and Phensydryl. Although it is nominally mandatory to have a prescription, it is a highly neglected rule, especially in smaller cities where prescriptions are ignored on a regular basis. Codeine phosphate tablets are also available over the counter, despite being prescription-only as well. They are among the most abused over-the-counter drugs in South Asia (across all sections of its society), and continue to be freely available despite legislations by States to curb their availability to buyers without prescriptions.
- Certain codeine products are encountered on the illicit market, frequently in combination with carisoprodol. Combinations of codeine and glutethimide (Doriden) used to be fairly commonplace, but are almost unheard of today, due to the withdrawal of glutethimide products from the marketplace in the US and almost all other countries.
- Codeine is also demethylated to illicitly synthesize morphine.[5]

Footnotes

1. ^ Schroeder K, Fahey T. "Over-the-counter medications for acute cough in children and adults in ambulatory settings.". Cochrane Database Syst Rev: CD001831. DOI:10.1002/14651858.CD001831. PMID 15495019.
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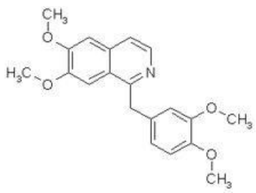
5. ^ Hogshire, Jim (June 1999). Pills-A-Go-Go: A Fiendish Investigation into Pill Marketing, Art, History & Consumption. Los Angeles: Feral House, 216-223. ISBN 0922915539.

See also

- Morphine

- Opioid
- Psychoactive drug

Papaverine



Systematic (IUPAC) name

1-[(3,4-dimethoxyphenyl)methyl]-6,7-dimethoxy-isoquinoline

Identifiers

CAS number 61-25-6

ATC code A03**AD01** G04**BE02**

PubChem 4680

DrugBank APRD00628

Chemical data

Formula C20H21NO4[1]

Mol. weight 339.385 g/mol[1]

Pharmacokinetic data

Bioavailability **80%[3]**

Protein binding ~90%

Metabolism Hepatic[3]

Half life 1.5-2 hours[3]

Excretion Renal[3]

Therapeutic considerations

Pregnancy cat. USA: C[4]

Routes Oral, intravenous, intramuscular, rectal,[5] intracavernosal

Papaverine is an opium alkaloid used primarily in the treatment of visceral spasm, vasospasm (especially those involving the heart and the brain), and occasionally in the treatment of erectile dysfunction[3]. While it is found in the opium poppy, papaverine differs in both structure and pharmacological action from the other opium alkaloids.

Uses

Papaverine is approved to treat spasms of the gastointestinal tract, bile ducts and ureter and for use as a cerebral and coronary vasodilator[3] in subarachnoid hemorrhage (combined with balloon angioplasty)[6] and coronary artery bypass surgery[7]. Papaverine may also be used as a smooth muscle relaxant in microsurgery where it is applied directly to blood vessels.

The in vivo mechanism of action is not entirely clear, but an inhibition of the enzyme phosphodiesterase causing elevation of cyclic AMP levels is significant. It may also alter mitochondrial respiration.

Side effects

Frequent side effects of papaverine treatment include polymorphic ventricular tachycardia, constipation, interference with sulphobromophthalein[8] retention test (used to determine hepatic function), increased transaminase levels, increased alkaline phosphatase levels, hyperbilirubinemia, somnolence, and vertigo[3].

Rare side effects include flushing of the face, hyperhidrosis (excessive sweating), cutaneous eruption, arterial hypotension, tachycardia, lack of appetite, jaundice, eosinophilia, thrombopenia, mixed hepatitis, headache, allergic reaction, chronic active hepatitis,[3] and paradoxical aggravation of cerebral vasospasm[9].

Formulations and Tradenames

Papaverine is available as a conjugate of hydrochloride, codecarboxylate, adenylate, and teprosylate[10]. It was also once available as a salt of hydrobromide, camsylate, cromesilate, nicotinate, and phenylglycolate. The hydrochloride salt is available for intramuscular, intravenous, rectal and oral administration.[5] The teprosylate is available in intravenous, intramuscular, and orally administered formulations[11]. The codecarboxylate is available in oral form, only,[12] as is the adenylate[13].

The codecarboxylate is sold under the name Albatran®,[14] the adenylate as Dicertan®,[15] and the hydrochloride salt is sold variously as Artegodan® (Germany), Cardioverina® (countries outside Europe and the United States), Dispamil® (countries outside Europe and the United States), Opdensit® (Germany), Panergon® (Germany), Paverina Houde® (Italy, Belgium), Pavacap (United States), Pavadyl® (United States), Papaverin-Hamelin® (Germany), Paveron® (Germany), Spasmo-Nit® (Germany),[5] Cardiospan®, Papaversan®, Cepaverin®, Cerespan®, Drapavel®, Forpaven®, Papalease®,

Pavatest®, Paverolan®, Therapav® (France[16]), Vasospan®, Cerebid®, Delapav®, Dilaves®, Durapav®, Dynovas®, Optenyl®, Pameion®, Papacon®, Pavabid®, Pavacen®, Pavakey®, Pavased®, Pavnell®, Alapav®, Myobid®, Vasal®, Pamelon®, Pavadel®, Pavagen®, Ro-Papav®, Vaso-Pav®, Papanerin-hcl®, Qua bid®, Papital T.R.®, Paptial T.R.®, Pap-Kaps-150®.[17]

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12. a Unknown (1998). PAPAVERINE CODECARBOXYLATE. Molécule(s) de base : PAPAVERINE. Biam. Retrieved on 26 September 2005. (French)
13. a Unknown (1998). PAPAVERINE ADENYLATE. Molécule(s) de base : PAPAVERINE. Biam. Retrieved on 26 September 2005. (French)
14. a SID 660773 PubChem Substance Summary. Retrieved on 25 September 2005. National Center for Biotechnology Information.

15. *a* SID 660767 -- PubChem Substance Summary. Retrieved on 25 September 2005. National Center for Biotechnology Information.

16. *a* THERAPAV (PRODUIT PUR) - Détail. Retrieved on 26 September 2005. CSST - Service du répertoire toxicologique. (French)

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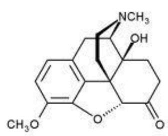
Semisynthetic opioids

Heroin | Oxycodone

Oxycodone



Systematic (IUPAC) name

4, 5-epoxy-14-hydroxy-3- methoxy-17-methylmorphinan-6-one

Identifiers

CAS number 76-42-6

ATC code N02**AA05**

PubChem 5284603

DrugBank APRD00387

Chemical data

Formula $C_{18}H_{21}NO_4$

Mol. weight 315.364 g/mol

Pharmacokinetic data

Bioavailability **Up to 87%**

Protein binding 45%

Metabolism Hepatic

Half life 3 - 4.5 hours

Excretion Urine

Therapeutic considerations

Pregnancy cat. B/D(prolonged use or in high doses at term)

Legal status Schedule I(CA) Class A(UK) Schedule II(US)

Dependence Liability Moderate - High

Routes Oral, intramuscular, intravenous, intranasally, subcutaneous, transdermal, rectal

Oxycodone is a potent and addictive opioid analgesic medication synthesized from thebaine. Its name is derived from codeine - the chemical structures are very similar, differing only in that the hydrogen on the codeine is oxidised to a hydroxyl group, hence 'oxy' and the hydroxyl group from the codeine becomes a ketone group, hence 'oxycodone.'

It is effective orally and is marketed in combination with acetylsalicylic acid (*Percodan*, *Endodan*, *Roxiprin*) or paracetamol/acetaminophen (*Percocet*, *Endocet*, *Roxicet*, *Tylox*) for the relief of pain. More recently, ibuprofen has been added to oxycodone (*Combunox*). It is also sold in a sustained-release form by Purdue Pharma under the trade name *OxyContin* as well as generic equivalents, and instant-release forms *Endone*, *OxyIR*, *OxyNorm*, *Percolone*, *OxyFAST*, and *Roxicodone*. Roxicodone is available in 5, 15, and 30 mg tablets. OxyContin is available in 10, 20, 40, 80, and 160 mg tablets, and, due to its sustained-release mechanism, is effective for eight to twelve hours. Outside the U.S. OxyContin is also available in a 5 mg tablet. (The 160 mg formulation was discontinued in May 2001.) OxyNorm is available in 5, 10, and 20 mg capsules and tablets; also as a 1 mg/1 ml liquid in 250 mg bottles and as a 10 mg/1 ml concentrated liquid in 100 mg bottles.

In the United States, oxycodone is a Schedule II controlled substance both as a single agent and in combination products containing paracetamol, ibuprofen or aspirin.

Chemical structure

The chemical structure of oxycodone is the methylether of oxymorphone: 3-Methyl-oxymorphone. It could also be described as 14-Hydroxy-Codeinone. It is principally supplied as its hydrochloride salt: oxycodone hydrochloride

Bioavailability

Oxycodone can be administered orally, intranasally, via intravenous/intramuscular/subcutaneous injection, or rectally. The bioavailability of intranasal administration averages between 46-47%, but can be as much as 75%. Oral oxycodone is the most efficient means of administration, having an absorbtion of 60-87%.

Rectal administration yields the same results. Injecting oxycodone will result in a stronger effect, and quicker onset, with a bioavailability slightly higher than oral administration.[1]

Medical use

Oxycodone is one of the most powerful medications for pain control that can be taken orally. Percocet tablets (Oxycodone with acetaminophen) are routinely prescribed for post-operative pain control. Oxycodone is also used in treatment of moderate to severe chronic pain. When used at recommended doses for relatively short periods (several weeks), it provides effective pain control with manageable side effects. Both immediate release oxycodone and sustained-release OxyContin are prescribed for pain due to cancer more than for any other condition. Due to an increase in cranial pressure, though clinically negligible, oxycodone is rarely recommended as a first-line treatment for medical issues of the head, including accidents involving brain trauma or spinal meningitis infections.

Nausea, constipation, lightheadedness, rash or itchiness, dizziness, and emotional mood disorders are the most frequently reported side effects. Other side-effects can also include slightly decreased testosterone levels in men. Misuse or long-term medical use of the drug can cause temporary impotence as well as a significant prostate enlargement in men.

Tolerance and physical dependence occurs after several days to weeks of treatment, with larger doses being required to achieve the same degree of analgesia.

According to the DEA and the companies that manufacture the drug, psychological addiction as a result of medical use is uncommon. Despite this statement, there are several lawsuits underway brought by plaintiffs who claim to have developed addiction as a result of medical use.

Several companies such as Elite Pharmaceuticals, Inc. and Pain Therapeutics, Inc are currently developing an anti-abuse version of oxycodone. Elite's ELI-216 has completed Phase I clinical trials and Pain Therapeutics' new drug called Remoxy is in Phase III clinical trials.

History

Oxycodone is an agonist opioid, and as such is a variation on an ancient theme beginning with the simple consumption or smoking of the alkaloid-bearing parts of Papaver somniferum, the opium poppy, first cultivated circa 3400 BC in lower Mesopotamia. Ancient Sumerians, Assyrians, Babylonians, and Egyptians found that smoking the extract derived from the seedpods yielded a pleasurable, peaceful feeling throughout the body. The Sumerians called the poppy plant "Hul Gil" or "joy plant". Cultivation and use spread quickly to the rest of the Levant and the Arabian Peninsula, eventually reaching India and China.

Oxycodone is a semi-synthetic opioid derived from the alkaloid thebaine, unlike most early opium-derived drugs which instead used the morphine or codeine alkaloids also found in the plant. Oxycodone was first synthesized in a German laboratory in 1916, a few years after the German pharmaceutical company Bayer had stopped the mass production of heroin due to addiction and abuse by both patients and physicians. It was hoped that a thebaine-derived drug would retain the analgesic effects of morphine and heroin with less of the euphoric effect which led to addiction and over-use. To some extent this was achieved, as oxycodone does not "hit" the central nervous system with the same immediate punch as heroin or morphine do and it does not last as long. The subjective experience of a "high" was

still reported for oxycodone, however, and it made its way into medical usage in small increments in most Western countries until the introduction of the OxyContin preparation radically boosted oxycodone use.

Abuse

The introduction of OxyContin in 1995 resulted in increasing patterns of abuse. Unlike Percocet, whose potential for abuse is limited by the presence of paracetamol, OxyContin contains only oxycodone and inert filler. Abusers wash off the coating and crush the tablets to defeat the time-release mechanism, then either ingest the resulting powder orally, intranasally, via intravenous/intramuscular/subcutaneous injection, or rectally to achieve rapid absorption into the bloodstream. Injection of OxyContin is particularly dangerous since it contains binders which enable the time release of the drug. Often mistaken as the time release, the outside coating of the pill is merely used as a color code for different dosage amounts. The vast majority of OxyContin-related deaths are attributed to ingesting substantial quantities of oxycodone in combination with another depressant of the central nervous system such as alcohol or benzodiazepines. While high doses of oxycodone can be fatal to an opiate-naïve individual in and of itself, this is (comparatively) rarely the case. It was once felt that "combination" opioids (those that contain one or more additional, non-narcotic ingredients) would be less subject to abuse, since, for example, the amount of paracetamol present in large overdoses of Percocet would cause stomach upset and liver damage. However, it has been demonstrated that abusers seeking the euphoric "high" are not deterred by these potential side effects or toxicities. Abusers soon discovered that extremely simple methods to separate the ingredients exist, particularly due to the widely disparate solubility of the alkaloids and analgesics in water ("cold water extraction").

Oxycodone has similar effects to morphine and heroin, and appeals to the same abuse community. Armed robberies of pharmacies where the robber demanded only OxyContin, not cash, have occurred. In some areas, particularly the eastern U.S., OxyContin has been the drug of greatest concern to enforcement authorities, although trustworthy data on the actual incidence of "Oxy abuse" have been difficult to establish.

Because oxycodone is highly regulated, when acquired illegally it is quite expensive. Black market prices in Washington, DC, and Portland, Maine, for example, have been reported to reach upwards of one dollar per milligram. In parts of Kentucky, particularly in Appalachia, nearly $1.25/mg. Legally acquired OxyContin is however rather expensive, costing as much as 400 US dollars for a normal month supply. Again, in mid-2006, brand-name or similar-quality generic (e.g., Watson, Purdue) eighty-milligram tablets sold for approximately twelve dollars whereas low-end generics (e.g., the above-referenced "footballs") scarcely pushed three dollars.

In Australia OxyContin is covered by the PBS, and a patient can get 3 boxes (60 tablets) for $4.70AUD in total. This has led to Federal tightening of restrictions from May 2006 (see Regulation below). The 20mg tablet can fetch $30AUD-$50AUD on the Gold Coast black market. As such there are professional "Doctor shoppers" making a tidy profit each week from OxyContin.

Like other opioids, oxycodone can be fatal at high doses or when combined with depressants such as alcohol. Several documented fatalities from OxyContin abuse have been

made public; however, these have done little to deter the combined use of the drug with depressants on account of the intense euphoria it produces.

In early 2006 on the East Coast there were multiple antectodal reports of "fake" OxyContin 80mg tablets, especially in Philadelphia and New York City. These fake OxyContin consistly mainly of sugar and were of poor quality, noting the distinct green color which differs from commercially made tablets. There have also been multiple reports of fake OxyContin 80mg tablets that contained Fentanyl.[2]

Conservative radio host Rush Limbaugh is a famous admitted former OxyContin addict and abuser[3]. Jason Mewes was also addicted to OxyContin whilst also abusing heroin until he became clean.

Illegal distribution of OxyContin occurs through pharmacy diversion, dishonest physicians, "doctor shopping," fake prescriptions, and robbery, all of which divert the pharmaceutical onto the illicit market. The increase of this situation coincides with the increase in the illegal use and abuse of this drug. The oxycodone contained in OxyContin produces opiate-like effects, and is considered a "reasonable substitute" for heroin[4]. The most commonly diverted dosages are the 40mg and 80mg strengths[4].

Manufacturer and Patents

OxyContin was first introduced onto the market by Purdue Pharma L.P. in 1995. This pharmaceutical company was founded in 1892 in New York City, and is currently a privately owned company that operates solely within the United States. The different branches within this company include, Purdue Pharma L.P., The Purdue Frederick Company, Purdue Pharmaceutical Products L.P., and Purdue Products L.P. (www.pharma.com). It has multiple patents for their drug OxyContin, but has recently been involved in a series of on going legal battles deciding on whether or not these patents are valid. On June 7th, 2005, the United States Court of Appeals upheld a decision from the previous year that some of Purdue's patents for OxyContin could not be enforced. This decision allowed and led to the immediate announcement from Endo Pharmaceutical Holdings, Inc. that they would begin launching a generic version of all four strengths of OxyContin[5]. Purdue, however, had already made negotiations with another pharmaceutical company (IVAX Pharmaceuticals) to distribute their brand OxyContin in a generic form. This contract was severed, and currently Watson Pharmaceuticals is the exclusive U.S. distributor of the generic versions of OxyContin Tablets. The agreement stipulates that "Purdue will manufacture and supply oxycodone HCI controlled-release tablets to Watson, which will market, sell, and distribute the authorized generic product in 10, 20, 40, and 80 milligram dosages in the United States"[6].

Purdue Pharma L.P. is based out of Stamford, Connecticut, and is the site of the company's headquarters. Manufacturing takes place at three different sites, which include: Purdue Pharmaceuticals L.P., a plant located in Wilson, North Carolina, The P.F. Laboratories Inc. in Totowa, New Jersey, and Rhodes Technologies L.P. located in Coventry, Rhode Island. Purdue Pharma L.P. also has research labs located in Cranbury, New Jersey. OxyContin is currently legally and illegally distributed throughout the U.S., Canada, and Mexico. Legal distribution takes place from the P.F. Laboratories Inc. in Totowa. Since the drug is a controlled substance, a prescription is required to obtain it, and is shown to be most frequently prescribed in the eastern U.S.[4]. Purdue also exports OxyContin to wholesale distributors in Mexico and

Canada. However, they have experienced increasing levels of illicit drug trafficking with the distribution outside of the U.S. that has led to certain responsive actions. The pill exported to Mexico is stamped with the letters "EX" instead of the customary "OC," and similarly the pills to Canada read "CDN." Purdue stopped exporting to Canada in 2001, and instead Canada imports the drug from a manufacturer in England. Despite these problems, OxyContin is one of the leading opioid painkillers on the market. In 2001, OxyContin was the highest sold drug of its kind, and in 2000, over 6.5 million prescriptions were written[7].

Chemistry

Oxycodone is made, commercially, from thebaine, a minor component of opium. The 14 hydroxy group increases potency by about 50% over hydrocodone. The 14 cinnamyl ester is 114x morphine in potency.

Regulation

Regulation of oxycodone (and opioids in general) differs according to country, with different places focusing on different parts of the "supply chain".

Regulation in the USA

Regulation of prescription drugs comes from many different areas. The Food and Drug Administration (FDA) approves drugs for medical use, as well as sets regulations for the marketing of drugs, including controlled substances. The Drug Enforcement Administration (DEA) on the other hand, receives its regulatory authority from the Controlled Substances Act (CSA) [21 U.S.C. §§ 801-971], which "mandates that DEA prevent, detect and investigate the diversion of legally manufactured controlled substances while, at the same time, ensuring that there are adequate supplies to meet the legitimate medical needs in the United States"[8].

Part of the regulation of prescription drugs is connected to their marketing and advertising. The FDA has authority over this sector under the Food, Drug, and Cosmetic (FD&C) Act and its implementing regulations. The Division of Drug Marketing, Advertising, and Communications (DDMAC) is "responsible for regulating prescription drug advertising and promotion," and has a "mission is to protect the public health by ensuring that prescription drug information is truthful, balanced, and accurately communicated"[9].

Regulation in Australia

In contrast, in Australia a General Practitioner can prescribe up to a 10 day supply of OxyContin, provided that they gain authority from Canberra for each prescription written. Prescriptions for a 30 day supply require two doctors, and must be cleared by Canberra. Additional prescriptions (i.e. for chronic pain or cancer patients) require two doctors for the first prescription, one of whom is a Pain Specialist, the treatment must have started within a hospital, and at least one of the prescribing doctors must be a designated as primary

prescriber by a Pain Specialist, and each prescription must be cleared by Canberra. Pharmacists must report the issuing of all oxycodone to the same authority in Canberra - mismatches found between prescribers, patients and Pharmacists result in investigation.

Advertising

Purdue Pharma L.P. does not use direct-to-consumer advertising, but instead focuses their marketing tactics towards health care professionals exclusively. They do this through the use of paper advertisements in medical journals and other publications of this nature, as well as promotion and sale directly to physicians, pharmacies, and hospitals. In January of 1996, Purdue signed a co-promotion agreement with Abbott in regards to their OxyContin Tablets. Abbott is now involved in the promotion of the drug to anesthesiologists and surgeons in hospitals throughout the U.S. (www.pharma.com). Although Purdue does not use direct-to-consumer advertising, OxyContin is becoming an increasingly more publicized and known drug to the general public. The discovery of its recreational benefits has led to an illicit underground market. As discussed earlier, due to acts such as pharmacy diversion and "doctor shopping" the drug is widely available to those without a prescription. The increased misuse of the drug has led to a higher number of emergency department mentions and deaths associated with oxycodone[4]. Despite the increased efforts by the FDA, DEA, and state/local authorities, along with this negative publicity of the drug is not stopping its illicit use, but instead seems to be fueling the underground market.

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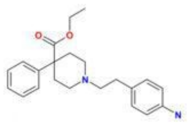
Synthetic opioids - Anileridine



Systematic (IUPAC) name ethyl1-[2-(4-aminophenyl)ethyl]- 4-phenyl-piperidine-4-carboxylate

Identifiers

CAS number 144-14-9

ATC code **N01**AH05

PubChem 8944

DrugBank APRD00741

Chemical data

Formula $C_{22}H_{28}N_2O_2$

Mol. weight 352.47 g/mol

Physical data

Melt. point 83 °C (181 °F)

Pharmacokinetic data

Protein binding > 95%
Anileridine (Leritine) is a synthetic opioid and strong analgesic medication.

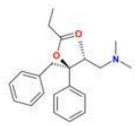
Administration

As tablets or injection.

Pharmacokinetics

Anileridine usually takes effect within 15 minutes of either oral or intravenous administration, and lasts 2-3 hours. It is mostly metabolized by the liver.

Dextropropoxyphene



Systematic (IUPAC) name

[(2R,3R)-4-dimethylamino- 3-methyl-1,2-diphenyl-butan-2-yl] propanoate

Identifiers

ATC code **N02**AC04

PubChem 10100

Chemical data

Formula C22H29NO2

Mol. weight 339.471

Dextropropoxyphene is an analgesic in the opioid category. It is used to treat mild to moderate pain and as an antitussive. It can be used to ease pain before, during and after an operation. It is often combined with acetominophen in the preparation co-proxamol (Darvocet in the US and CAPADEX in AUS).

It is an optical isomer of Levopropoxyphene. The racemic mixture is called Propoxyphene.

Some preparations that contain dextropoxyphene include: Distalgesic and Doloxene.

Indications

Analgesia

Dextropropoxyphene, like codeine, is a "weak" opioid. Codeine is more commonly used, however some individuals (approximately 10-20% of the Caucasian population) are unable to metabolize it, due to poor functioning of the enzyme CYP2D6. It is in these people that dextropropoxyphene is particularly useful, as its metabolism does not require CYP2D6.

Opioid withdrawal

In pure form, dextropropoxyphene is commonly used to ease the withdrawal symptoms in people addicted to opioids. Being very weak in comparison to the opioids that are

commonly abused, dextropropoxyphene can only act as a "partial" substitute. It does not have much effect on mental cravings; however it can be effective in alleviating physical withdrawal effects, such as muscle cramps.

Dextropropoxyphene is subject to some controversy: while many physicians prescribe it for a wide range of mildly to moderately painful symptoms as well as for treatment of diarrhoea, many others refuse to prescribe it, citing its highly addictive nature and limited effectiveness (some studies show it to be no more effective as a painkiller than aspirin).

The therapeutic index of dextroproxyphene is relatively small. In the UK, dextropropoxyphene and co-proxamol are now discouraged from general use; and, since 2004, preparations containing only dextropropoxyphene have been discontinued. This has been a somewhat controversial decision, since it has caused abusers to switch to the combined product and risk acetominophen toxicity. Australia declined to follow suit and opted to allow pure dextropropoxyphene to remain available by prescription.

In the United States, dextropropoxyphene HCl is available as a prescription formulation with acetaminophen in ratio anywhere from 30mg / 600mg to 60mg / 325mg, respectively. These are usually named "Darvocet." On the other hand, "Darvon" is a pure Propoxyphene preparation available in the U.S. that does not contain acetominophen. In Australia, dextropropoxyphene is available on prescription, both as a combined product (32.5mg dextropropoxyphene per 325mg acetaminophen) known as either "Di-gesic", "Capadex", or "Paradex," and in pure form (100mg capsules) known as "Doloxene".

Adverse effects

Darvocet overdose is commonly broken into two categories: liver toxicity (from acetaminophen poisoning) and dextropropoxyphene overdose. Many users experience toxic effects from the acetaminophen in pursuit of the endlessly-increasing dose required to achieve euphoria. They suffer acute liver toxicity, which causes severe stomach pain, nausea, and vomiting (all of which are increased by light or stimulation of the sense of sight).

Dextropropoxyphene also has several other non-opioid side-effects.

Both propoxyphene and it's metabolite norpropoxyphene, have local anesthetic effects at concentrations about 10 times those necessary for opioid effects. In this respect, norpropoxyphene is more potent than propoxyphene, and they are both more potent than lidocaine.[1]

Both propoxyphene and norpropoxyphene also have direct cardiac effects which include decreased heart rate, decreased contractility, and decreased electrical conductivity (ie, increased PR, AH, HV, and QRS intervals). Norpropoxyphene is several times more potent than propoxyphene in this activity. These effects appear to be due to their local anesthetic activity and are not reversed by naloxone.[1][2][3]

Both propoxyphene and norpropoxyphene are potent blockers of cardiac membrane sodium channels and are more potent than lidocaine, quinidine, and procainamide in this respect.[4]

They (propoxyphene and nor-propoxyphene) appear to have the characteristics of a Vaughn Williams Class IC antiarrhythmic.

Toxicologic Mechanism

A) Excessive opioid receptor stimulation is responsible for the CNS depression, respiratory depression, miosis, and gastrointestional effects seen in propoxyphene poisoning. It may also account for mood/thought altering effects.

B) Local anesthetic activity appears to be responsible for the arrhythmias and cardiovascular depression seen in propoxyphene poisoning.[3] Widening of the QRS complex appears to be a result of a quinidine-like effect of propoxyphene, and sodium bicarbonate therapy appears to have a positive direct effect on the QRS dysrhythmia.[5]

C) Seizures may result from either opioid or local anesthetic effects.[1]

D) Pulmonary edema may result from direct pulmonary toxicity, neurogenic/anoxic effects, or cardiovascular depression.[3]

Recreational use

Recreational users tend to take anywhere from 240 to 420 milligrams of dextropropoxyphene (and the acetaminophen that goes with it). These users often suffer a persistent dry mouth, decreased appetite, urinary retention and constipation that may lead to diverticulitis.

Dextropropoxyphen Hydrochloride is also used in the so-called "Darvon cocktail"

References

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5. ^ Stork et al., 1995

Endorphins

Endorphins (or more correctly Endomorphines) are endogenous opioid biochemical compounds. They are peptides produced by the pituitary gland and the hypothalamus in vertebrates, and they resemble the opiates in their abilities to produce analgesia and a sense of well-being. In other words, they might work as "natural pain killers." Using drugs may increase the effects of the endorphins.

The term "endorphin" implies a pharmacological activity (analogous to the activity of the corticosteroid category of biochemicals) as opposed to a specific chemical formulation.

History

These opioid neuropeptides were first discovered in 1975 by two independent groups of investigators. John Hughes and Hans Kosterlitz of Scotland isolated — from the brain of a pig — what they called "enkephalins" (from the Greek µ½ºÆ±»¿Â, cerebrum). Around the same time in the calf brain, Rabi Simantov and Solomon H. Snyder of the United States found what Eric Simon (who independently discovered opioid receptors in the brain) later termed "endorphin" by an abbreviation of "endogenous morphine", which literally means "morphine produced naturally in the body". In fact, morphine itself is not a peptide. However, recent studies have demonstrated that diverse animals and human tissues can produce morphine.

Molecular biology

There are at least three different families of opioid peptides. The endorphins are products of a gene that encodes a large precursor peptide called pro-opiomelanocortin (POMC); POMC is expressed in the pituitary gland and in the arcuate nucleus of the hypothalamus. The best-known endorphins are ±-, ^{2}- and ^{3}-endorphin, of which *^{2}-endorphin* appears to be most implicated in pain relief.

The amino acid residue sequence (primary structure) of ^{2}-endorphin is:

Tyr-Gly-Gly-Phe-Met-Thr-Ser-Glu-Lys-Ser-Gln-Thr-Pro-Leu-Val-Thr-Leu-Phe-Lys-Asn-Ala-Ile-Ile-Lys-Asn-Ala-Tyr-Lys-Lys-Gly-GluOH (Fries, 2002).

Other opioid peptides are the enkephalins and the dynorphins. The term enkephalin mainly refers to two peptides, [Met]-enkephalin and [Leu]-enkephalin, which are both products of the proenkephalin gene. [Met]-enkephalin is Tyr-Gly-Gly-Phe-Met. [Leu]-enkephalin has Leu in place of Met. Dynorphin is the product of a third opioid gene, called prodynorphin.

Mechanism of action

Beta-endorphin is released into the blood (from the pituitary gland) and into the spinal cord and brain from hypothalamic neurons. The beta-endorphin that is released into the blood cannot enter the brain in large quantities because of the blood-brain barrier. The physiological importance of the beta-endorphin that can be measured in the blood is far from clear: beta-endorphin is a cleavage product of POMC which is the precursor hormone for adrenocorticotrophic hormone (ACTH), so it will be released whenever ACTH is released. The behavioural effects of beta-endorphin are exerted by its actions in the brain and spinal cord, and probably the hypothalamic neurons are the major source of beta-endorphin at these sites.

Beta-endorphin has the highest affinity for the Mu1-opioid receptor, slightly lower affinity for the Mu2 and Delta-opioid receptors and low affinity for the Kappa1-opioid receptors. Mu receptors are the main receptor through which morphine acts. Classically, Mu receptors are presynaptic, and inhibit neurotransmitter release; through this mechanism, they inhibit the release of the inhibitory neurotransmitter GABA, and disinhibit the dopamine pathways, causing more dopamine to be released. By hijacking this process, exogenous opioids cause inappropriate dopamine release, and lead to aberrant synaptic plasticity which causes addiction. Opioid receptors have many other and more important roles in the brain and periphery however, modulating pain, cardiac, gastric and vascular function as well as possibly panic and satiation, and receptors are often found at postsynaptic locations as well as presynaptically

Activity

Scientists debate whether specific activities release measurable levels of endorphins. Much of the current data comes from animal models which may not be relevant to humans.

The studies that do involve humans often measure endorphin plasma levels, which do not necessarily correlate with levels in the CNS. Other studies use an opioid antagonist, usually naloxone, to indirectly measure the release of endorphins by observing the changes that occur when any endorphin activity that might be present is blocked.

Capsaicin (the active chemical in chili peppers) also has been shown to stimulate endorphin release. Topical capsaicin has been used as a treatment for certain types of chronic pain.

The placebo effect has been linked to endorphins. In one study, a volunteer received pain by a compression cuff on his arm. In the first trial, no drug was administered and the patient showed signs of pain including facial grimace, increased blood pressure, and sweating. During the next trial, the physician informed the volunteer that he would be injected with morphine and that he would feel no pain. The morphine was injected, the pain compression repeated, and this time the volunteer showed and reported no pain. The morphine and compression was repeated several times. Then, the volunteer was unknowingly injected with a saline placebo, but still reported no sign of pain, though the last time he was unmedicated the signs of pain were obvious. In a last test, the patients' 'morphine' was actually an injection of naloxone, an opioid antagonist. Even though the volunteer believed the shot was morphine and expected relief, the endorphins' effect was blocked by the naloxone injection and the volunteer displayed the same signs of pain as the first unmedicated trial. (Groopman 169)

Another widely publicized effect of endorphin production is the so-called "*runner's high*", which is said to occur when strenuous exercise takes a person over a threshold that activates endorphin production. Endorphins are released during long, continuous workouts, when the level of intensity is between moderate and high, and breathing is difficult. This also corresponds with the time that muscles use up their stored glycogen and begin functioning with only oxygen. Workouts that are most likely to produce endorphins include running, swimming, cross-country skiing, long distance rowing, bicycling, aerobics, or playing a sport such as basketball, soccer, or football. However, some scientists question the mechanisms at work, their research possibly demonstrating the high comes from completing a challenge rather than as a result of exertion. (Klosterman) (Altman) There is some recent evidence that endogenous cannabinoids are responsible for "runner's high", rather than endorphins. (Endocannabinoids and exercise, by A Dietrich and W F McDaniel, May 4, 2004 bjsportsmed.com). Studies in the early 1980's cast doubt on the relationship between endorphins and the runner's high. There were a couple of reasons for this doubt. The first was that when an antagonist (pharmacological agent that blocks the action for the substance under study) was infused (eg naloxone) or ingested (naltrexone) the same changes in mood state occurred that happened when the person exercised with no blocker. A second piece of evidence is much more simple. It turns out that scientists cannot make a runner's high occur in the lab with any certainty. This makes it very difficult to study much less prove that endorphins cause the runners high.

In 1999, clinical researchers reported that inserting acupuncture needles into specific body points triggers the production of endorphins [2]. In another study, higher levels of endorphins were found in cerebrospinal fluid after patients underwent acupuncture. In addition, naloxone appeared to block acupuncture's pain-relieving effects. However, skeptics

say that not all studies point to that conclusion, and that in a trial of chronic pain patients, endorphins did not produce long-lasting relief. (Margolis 140-141).

The good feeling one gets from eating chocolate, smiling, laughing, sunbathing, being massaged, meditating, singing, listening to one's favorite music, or having an orgasm is partially attributed to the release of endorphins. [3]

References

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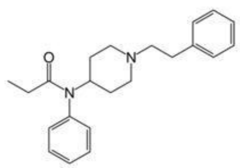
Fentanyl



Systematic (IUPAC) name

N-(1-(2-phenylethyl)-4-piperidinyl)-N-phenyl-propanamide

Identifiers

CAS number 437-38-7

ATC code N01**AH01** N02**AB03**

PubChem 3345

DrugBank APRD00347

Chemical data

Formula C***22***H***28***N***2***O

Mol. weight 336.471 g/mol

Physical data

Melt. point 87.5 °C (190 °F)

Pharmacokinetic data

Bioavailability 92% (transdermal), 50% (buccal)

Protein binding 80-85%

Metabolism hepatic, primarily CYP3A4

Half life 7 (range 3-12) hours

Therapeutic considerations

Pregnancy cat. $C_{(US)}$

Legal status Schedule $II_{(US)}$

Routes TD, IM, IV, oral, sublingual, buccal

Fentanyl is an opioid analgesic, first synthesized by Janssen Pharmaceutica (Belgium) in the late 1950s, with an analgesic potency of about 80 times that of morphine. Fentanyl was introduced into medical practice in the 1960s as an intravenous anesthetic under the trade name of Sublimaze. Fentanyl has an LD50 of 3.1 milligrams per kilogram in rats. The LD50 in humans is not known. Fentanyl is a Schedule II drug.

Synthesis

The synthesis of fentanyl (N-phenyl-N-(1-phenethyl-4-piperidinyl)propanamide) by Janssen Pharmaceutica was achieved in four steps, starting from 4-piperidinone hydrochloride. The 4-piperidinone hydrochloride was first reacted with phenethyl bromide to give N-phenethyl-4-piperidinone (NPP). Treatment of the NPP intermediate with aniline followed by reduction with sodium borohydride afforded 4-anilino-N-phenethyl-piperidine (ANPP). A final reaction between ANPP and propionic anhydride led to the fentanyl with a 47% overall yield.

Analogues

The pharmaceutical industry has developed several analogues of fentanyl:

- Alfentanil (Alfenta), an ultra-short acting (5–10 minutes) analgesic,
- Sufentanil (Sufenta), a potent analgesic (5 to 10 times more potent than fentanyl) for use in heart surgery.
- Remifentanil, currently the shortest acting opioid, has the benefit of rapid offset, even after prolonged infusions.
- Carfentanil (Wildnil) is an analogue of fentanyl with an analgesic potency 10,000 times that of morphine and is used in veterinary practice to immobilize certain large animals.

Therapeutic use

All forms of fentanyls are to be used only by opioid-tolerant patients; several deaths have occurred when used by other patients. Today, fentanyls are extensively used for anesthesia and analgesia. Duragesic, by Janssen Pharmaceutica, is a fentanyl transdermal patch used in chronic pain management. Duragesic patches work by releasing fentanyl into subcutaneous fats, which then slowly release the drug into the blood stream over 72 hours, allowing for long lasting relief from pain. In the past few years, the patches have gone generic and are available for lower costs. Duragesic is manufactured in five patch sizes: 12.5 μg/h, 25 μg/h, 50 μg/h, 75 μg/h, and 100 μg/h. Dosage is based on the size of the patch, since the transdermal absorption rate is generally constant at a constant skin temperature. Rate of absorption is dependent on a number of factors. Body temperature, skin type and placement of the patch can have major effects. The different delivery systems used by different makers will also affect individual rates of absorption.

Actiq, by Cephalon, is a recently-developed solid formulation of fentanyl citrate on a stick in the form of a lollipop that dissolves slowly in the mouth for transmucosal absorption. Actiq is intended for opioid-tolerant individuals and is effective in treating breakthrough cancer pain. It is also useful for breakthrough pain for those suffering bone injuries, severe back pain, neuropathy, arthritis, and some other examples of chronic nonmalignant pain. The unit is a berry-flavored lozenge on a stick which is swabbed on the mucosal surfaces inside the mouth—inside of the cheeks, under and on the tongue and gums—to release the fentanyl quickly into the system. It is most effective when the lozenge is consumed in 15 minutes. The drug is less effective if swallowed, absorption from the alimentary tract being poor. Actiq is available in six dosages, from 200 to 1600 μg in 200 μg increments (excluding 1000 μg and 1400 μg). Actiq is now available in the United states in generic form[1], through an FTC consent agreement[2].

FENTORA™ is a new delivery method of fentanyl; it is an effervescent tablet placed in the cheek and is absorbed through the buccal mucosa. It was introduced on 2006-09-25[3]. One advantage of FENTORA is quicker absorption into the bloodstream at lower dosage levels according to the prescribing information[4].

Fentanyl is frequently given intrathecally as part of spinal anesthesia or epidurally for epidural anesthesia and analgesia.

Illicit use

Illicit use of pharmaceutical fentanyls first appeared in the mid-1970s in the medical community and continues in the present. United States authorities classify fentanyl as a narcotic. To date, over 12 different analogues of fentanyl have been produced clandestinely and identified in the U.S. drug traffic. The biological effects of the fentanyls are similar to those of heroin, with the exception that there is less of a euphoric 'high' associated with the drug and a stronger analgesic effect. Additionally, fentanyl may be hundreds of times more potent — though in some places, it is sold as heroin, often leading to overdoses. Fentanyl also has a shorter half-life than that of heroin, and is most commonly used orally, but like heroin, can also be smoked, snorted or injected.

Actiq has appeared on the streets under the street name of "percopop". The pharmacy retail price ranges from US$16 to US$50 per unit (based on strength of lozenge), with the black market cost is anywhere from US$20 to US$60 per unit, depending on the strength.

Some heroin dealers mix fentanyl powder with larger amounts of heroin in order to increase potency or compensate for low-quality heroin, and to increase the volume of their product. As of late May 2006, a mix of fentanyl and either cocaine or heroin has caused an outbreak in overdose deaths in the United States, heavily concentrated in the cities of Detroit, Philadelphia, Milwaukee, Camden, Chicago,[5], and Little Rock. The mixture of fentanyl and heroin is known as "magic", among other names, on the street. [6]

Both Actiq and Duragesic are becoming as popular as OxyContin in pharmacy burglaries and robberies. In the U.S., law enforcement agencies are being instructed in how to tell the difference between Actiq and other medications so they are better able to notice abuse of the drug.

Several large quantities of illicitly-produced fentanyl have been seized by U.S. law enforcement agencies. In June 2006, 945 grams of 83%-pure fentanyl powder were seized by Border Patrol agents in California from a vehicle which had entered from Mexico. Mexico is the source of much of the illicit fentanyl for sale in the U.S. However, there has been one domestic fentanyl lab discovered by law enforcement, in April 2006 in Azusa, CA. The lab was a source of counterfeit 80 mg OxyContin tablets containing fentanyl instead of oxycodone, as well as bulk fentanyl and other drugs.[8],[9]

The "china white" form of fentanyl refers to the clandestinely produced alpha-methyl strain (AMF) [10] . This has been reported in the literature to be twice the strength of regular fentanyl. The main bonus of the alpha-methyl is it provides a site of resistance to metabolic degradation resulting in a drug with an increased duration [11].

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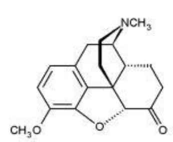
See also

- Psychoactive drug
-

Hydrocodone



Systematic (IUPAC) name

4,5a-Epoxy-3-methoxy-17-methylmorphinan-6-one tartrate (1:1) hydrate (2:5)

Identifiers

CAS number 125-29-1

ATC code R05**DA03**

PubChem 5284569

DrugBank APRD00591

Chemical data

Formula C***18***H***21***NO***3***

Mol. weight 299.368

Pharmacokinetic data

Metabolism Hepatic

Half life 4-8 hours

Therapeutic considerations

Pregnancy cat. Category C (USA)

Legal status Class A (UK), Schedule III (USA)

Routes Oral

Hydrocodone or *dihydrocodeinone* (marketed as *Vicodin*, *Anexsia*, *Dicodid*, *Hycodan*, *Hycomine*, *Lorcet*, *Lortab*, *Norco*, *Novahistex*, *Hydroco*, *Tussionex*, *Vicoprofen*) is a semi-synthetic opioid derived from two of the naturally occurring opiates, codeine and thebaine. Hydrocodone is an orally active narcotic analgesic and antitussive. Sales and production of this drug have increased significantly in recent years, as have diversion and illicit use. Hydrocodone is commonly available in tablet, capsule and syrup form.

Acetaminophen 650mg

As a narcotic, hydrocodone relieves pain by binding to opioid receptors in the brain and spinal cord. It may be taken with or without food. When taken with alcohol, it can intensify drowsiness. It may interact with monoamine oxidase inhibitors, as well as other drugs that cause drowsiness. It is in FDA pregnancy category C: its effect on an embryo or fetus is not clearly known and pregnant women should consult their physicians before taking it. Common side effects include dizziness, lightheadedness, nausea, drowsiness, euphoria, vomiting, and constipation. Some less common side effects are allergic reaction, blood disorders, changes in mood, mental fogginess, anxiety, lethargy, difficulty urinating, spasm of the ureter, irregular or depressed respiration and rash.

Hydrocodone can be habit-forming, and can lead to physical and psychological addiction. In the U.S., pure hydrocodone and forms containing more than 15 mg per dosage unit are considered Schedule II drugs. Those containing less than or equal to 15 mg per dosage unit in combination with acetaminophen or another non-controlled drug are called hydrocodone compounds and are considered Schedule III drugs. Hydrocodone is typically found in combination with other drugs such as paracetamol (acetaminophen), aspirin, ibuprofen and homatropine methylbromide. The purpose of the non-controlled drugs in combination is often twofold. 1) To provide increased analgesia via drug synergy. 2) To limit the intake of hydrocodone by causing unpleasant and often unsafe side effects at higher than prescribed doses (See Below). In the UK it is listed as a Class A drug under the Misuse of Drugs Act 1971.

Overdosing risks

The presence of acetaminophen in hydrocodone-containing products deters many drug users from taking excessive amounts. However, some users will get around this by extracting a portion of the acetaminophen using hot/cold water, taking advantage of the water-soluble element of the drug. It is not uncommon for addicts to have liver problems from consuming excessive amounts of acetaminophen over a long period of time; taking 10,000 to 15,000 milligrams (10 to 15 grams) of acetaminophen in a period of 24 hours typically results in severe hepatotoxicity, and doses in the range of 15,000-20,000 milligrams a day have been reported as fatal.[1] It is this factor that leads many addicts to use only single entity opiates such as OxyContin.

Daily consumption of hydrocodone should not exceed 40 milligrams in patients not tolerant to opiates. However, the 2006 PDR (Physicians Desk Reference) clearly states that Norco 10, containing 10 milligrams of hydrocodone and 325 milligrams of APAP (viz., acetaminophen or paracetamol), can be taken at a dosage of up to twelve tablets per day (120 milligrams of hydrocodone). Such high amounts of hydrocodone are *only* intended for opiate-tolerant patients, and titration to such levels must be monitored very carefully. This restriction is only limited by the fact that twelve tablets, each containing 325 milligrams of APAP, puts the patient right below the 24-hour FDA maximum of 4,000 mg of APAP. Some specially compounded products are routinely given to chronic pain patients in doses of up to 180 mg of hydrocodone per day. Tolerance to this drug can increase very rapidly if abused. Because of this, addicts often overdose from taking handfulls of pills, in pursuit of the high they experienced very early on in their hydrocodone use. Symptoms of hydrocodone overdosage include respiratory depression, extreme somnolence, coma, stupor, cold and/or clammy skin, sometimes bradycardia, and hypotension. A severe overdose may involve circulatory collapse cardiac arrest and/or death.

Alcohol

It is not recommended to mix any amount of hydrocodone with any amount of alcohol as doing so could cause health problems. APAP is metabolized solely by the liver. Therefore the risk of fatal overdose due to hepatotoxicity can occur with significantly lower levels of APAP when mixed with ethanol. This fact is often neither known nor given credence as it does not stop people from mixing them due to the feeling of euphoria it provides.

Commercial medications containing hydrocodone

When sold commercially, hydrocodone often is combined with another medication. Those combined with acetaminophen are known by various trademark names, such as Vicodin and Lortab. Hydrocodone also can be combined with aspirin (e.g., Lortab ASA), ibuprofen (e.g., Vicoprofen), and certain antihistamines (e.g., Chemdal HD).

Below are some of the commercially available medications containing hydrocodone, listed by manufacturer.

Abbott Laboratories

Dosage - Appearance - Trademark Name

5mg (500mg acetaminophen) - White tablets bisected on one side and debossed "VICODIN" on the other side - Vicodin

7.5mg (750mg acetaminophen) - White tablets with tapered edges bisected on one side and debossed "VICODIN ES" on the other side - Vicodin ES

10mg (660mg acetaminophen) - White tablets bisected on one side and debossed "VICODIN HP" on the other side - Vicodin HP

7.5mg (200mg ibuprofen) - Round white tablets debossed on one side with "VP" above the Abbott logo (a stylized, lower case "a") and blank on the other side - Vicoprofen

UCB Pharma

Dosage - Appearance - Trademark Name

2.5mg (500mg acetaminophen) - White tablets with red specs bisected and debossed "901" on one side and debossed "UCB" on the other side - Lortab

5mg (500mg acetaminophen) - White tablets with blue specs bisected and debossed "902" on one side and debossed "UCB" on the other side - Lortab

7.5mg (500mg acetaminophen) - White tablets with green specs bisected and debossed "903" on one side and debossed "UCB" on the other side - Lortab

10mg (500mg acetaminophen) - Pink tablets bisected and debossed "910" on one side and debossed "UCB" on the other side - Lortab

5mg (500mg aspirin) - Red tablets mottled with white and debossed "500" on one side and (possibly?) debossed "UCB" on the other side - Lortab ASA

7.5mg per 15mL (500mg acetaminophen) - Yellow, tropical-punch flavored liquid with 7% alcohol - Lortab Elixir

Watson Pharmaceuticals, Inc.

(NOTE: Watson manufactures under its own Trademarks and generic Trademark Equivalents)

Dosage - Appearance - Trademark Name

10mg (750mg acetaminophen) - Yellow Capule-shaped bisected on one side and debossed "Maxidone 634" on the other side - Maxidone®

5mg (325mg acetaminophen) - White tablets with orange specks bisected and debossed "Watson" on one side and "Watson 913" on the other side - Norco® 5/325

7.5mg (325mg acetaminophen) - Light orange oblong tablets bisected on one side and debossed "NORCO 729" on the other side - Norco® 7.5/325

10mg (325mg acetaminophen) - Yellow tablets bisected on one side and debossed "NORCO 539" on the other side - Norco®

Dosage - Appearance - Trademark Equivalent
2.5mg (500mg acetaminophen) - White tablets bisected on one side and debossed "WATSON 388" on the other side - Lortab®

5mg (325mg acetaminophen) - White tablets with orange specks bisected and debossed "Watson" on one side and "3202" on the other side - Norco® 5/325

5mg (500mg acetaminophen) - White oblong tablets bisected on one side and debossed "WATSON 349" on the other side - Vicodin®

7.5mg (325mg acetaminophen) - Light orange oblong tablets bisected on one side and debossed "WATSON 3203" on the other side - Norco® 7.5/325

7.5mg (500mg acetaminophen) - White tablets bisected on one side and debossed "WATSON 385" on the other side - Lortab®

7.5mg (650mg acetaminophen) - Pink tablets bisected on one side and debossed "WATSON 502" on the other side - Lorcet Plus®

7.5mg (750mg acetaminophen) - White tablets bisected on one side and debossed "WATSON 387" on the other side - Vicodin ES®

10mg (325mg acetaminophen) - Yellow tablets bisected on one side and debossed "WATSON 853" on the other side - Norco®

10mg (500mg acetaminophen) - Blueish/purple tablets bisected on one side and debossed "WATSON 540" on the other. - Lortab®

10mg (650mg acetaminophen) - Light green tablets bisected on one side and debossed "WATSON 503" on the other side - Lorcet 10/650®

10mg (660mg acetaminophen) - White tablets bisected on one side and debossed "WATSON 517" on the other side - Generic

10mg (750mg acetaminophen) - Yellow tablets bisected on one side and debossed "WATSON 3228" on the other side - Maxidone®

Mallinckrodt Pharmaceuticals

Dosage - Appearance - Trademark Name

5mg (325mg acetaminophen) - White tablets bisected on one side and debossed "M365" on the other side - Generic

5mg (500mg acetaminophen) - White tablets bisected on one side and debossed "M357" on the other side - Generic

7.5mg (325mg acetaminophen) - White tablets bisected on one side and debossed "M366" on the other side - Generic

7.5mg (500mg acetaminophen) - White tablets bisected on one side and debossed "M358" on the other side - Generic

7.5mg (650mg acetaminophen) - White tablets bisected on one side and debossed "M359" on the other side - Generic

7.5mg (750mg acetaminophen) - White tablets bisected on one side and debossed "M360" on the other side - Generic

10mg (325mg acetaminophen) - White tablets bisected on one side and debossed "M367" on the other side - Generic

10mg (500mg acetaminophen) - White tablets bisected on one side and debossed "M363" on the other side - Generic

10mg (650mg acetaminophen) - Blue tablets bisected on one side and debossed "M361" on the other side - Generic

10mg (660mg acetaminophen) - White tablets bisected on one side and debossed "M362" on the other side - Generic

10mg (750mg acetaminophen) - White tablets bisected on one side and debossed "M364" on the other side - Generic

Laudanum

Laudanum is an opium tincture, sometimes sweetened with sugar and also called wine of opium.

History

In the 16th century, Paracelsus experimented with the medical value of opium. He decided that its medical (analgesic) value was of such magnitude that he called it Laudanum,

from the Latin laudare, to praise, or from labdanum, the term for a plant extract. He did not know of its addictive properties.

In the 19th century, laudanum was used in many patent medicines to "relieve pain... to produce sleep... to allay irritation... to check excessive secretions... to support the system... [and] as a sudorific". The limited pharmacopoeia of the day meant that opium derivatives were among the most efficacious of available treatments, and so laudanum was widely prescribed for ailments from colds to meningitis to cardiac diseases, in both adults and children.

The Romantic and Victorian eras were marked by the widespread use of laudanum in Europe, and the United States. Initially a working class drug, laudanum was cheaper than a bottle of gin or wine, because it was treated as a medication for legal purposes and not taxed as an alcoholic beverage. Notable addicted literary figures include: Edgar Allan Poe; Samuel Taylor Coleridge, who was addicted for much of his adult life; Thomas de Quincey, who turned his addiction into literary success with the publication of Confessions of an English Opium Eater; Lord Byron; Percy Bysshe Shelley, who suffered raging laudanum-induced hallucinations; John Keats; Iolo Morgannwg, the Welsh antiquarian; Charles Dickens; Antonin Artaud; and Charles Baudelaire[citation needed]. There were also political figures, such as William Wilberforce and Meriwether Lewis, who used the drug.

Innumerable Victorian women were prescribed the drug for relief of menstrual cramps and vague aches and used it to achieve the pallid complexion associated with tuberculosis (frailty and paleness were particularly prized in females at the time). Nurses also spoon-fed laudanum to infants.

Featurings in fiction

In Literature

- In the Aubrey–Maturin series of novels, the ship's surgeon, Stephen Maturin, both uses the drug professionally and battles his own addiction to it.
- In Alan Moore's The League of Extraordinary Gentlemen, Allan Quatermain, opium-addicted, uses his bottle of laudanum to paralyze Edward Hyde.
- In Joanne Harris's 1993 novel Sleep Pale Sister, Effie was fed laudanum to keep her out of "hysterics" and also so that she could sleep.
- The character of Oscar Hopkins in Peter Carey's novel Oscar and Lucinda (1988) uses laudanum, initially under duress, to dull his hydrophobia during his expedition from Sydney.
- Mary Shelley's character Victor Frankenstein uses laudanum to help him sleep after the death of his friend, Henry Clerval.
- In Jack Finney's Time and Again, the main character, Si Morley, wonders if a live baby in a 1882 display case has been "doped up with one of the laudanum preparations I'd seen advertised in Harpers."
- Laudanum is also used as a means to circumvent Speck magic in the Soldier Son Trilogy by Robin Hobb.

- Laudanum is mentioned frequently in William S. Burroughs' Naked Lunch, and The Soft Machine Trilogy.
- In the tenth chapter of James Joyce's Ulysses, Haines is depicted drinking laudanum from a phial **[1]**.
- In Octavia Butler's "Kindred" Rufus' Mother uses laudanum as a medicine to relieve her pain and sorrow
- Laudanum is also mentioned in the song "A Legionnaire's lament" by the Decemberists.
- In Wilkie Collins' "The Moonstone" [1868], a valuable diamond, the Moonstone, is stolen by a character in a laudanum induced stupor.

In Film

- In the 2001 movie From Hell laudanum plays an important role: Jack the Ripper is shown using it to numb his victims while Inspector Frederick Abberline (played by Johnny Depp) is addicted to a laudanum and absinthe mixture.
- In the movie Tombstone, Wyatt Earp's wife is addicted to laudanum.
- In Interview with the Vampire (book and film) Claudia gives a laudanum and absinthe mixture to a small boy, on whom Lestat then feeds and becomes quite weak.
- In John Wayne's final movie The Shootist, his character J.B. Books is suffering from terminal cancer, and his doctor E.W. Hostetler (played by James Stewart) prescribes Laudanum to relieve the pain.
- In the upcoming movie "Amazing Grace, The William Wilberforce Story" there are numerous scenes of Wilberforce being given Laudanum to relieve symptoms of Colitis.

In Television

- Alma Garrett (played by Molly Parker) was addicted to laudanum in Deadwood.

Today's status

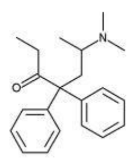
Laudanum is still available by prescription in the United States. It is classified as a Schedule II drug under the Controlled Substances Act. Its most common formulation is known as "deodorized tincture of opium," (or DTO), and is manufactured in the United States by Ranbaxy Pharmaceuticals. Deodorized or "denarcotized" opium means that narcotine, one of the most prevalent alkaloids in opium, has been removed, usually by a petroleum distillate. Narcotine has no analgesic properties, and frequently causes nausea and stomach upset; hence the preference for denarcotized opium.

The only medically-approved uses for laudanum in the United States are for treating diarrhea and pain. Laudanum, as deodorized opium tincture, contains the equivalent of 10

milligrams of morphine per milliliter. By contrast, laudanum's weaker cousin, paregoric, also known as camphorated tincture of opium, is 1/25th the strength of laudanum, containing only 0.4 milligrams of morphine per milliliter. Caution should be employed so as not to confuse opium tincture (laudanum) and camphorated opium tincture (paregoric), since overdose may occur if the former is used when the latter has been indicated. The United States Pharmacopia recommends that the abbreviation "DTO" never be used in place of "deodorized tincture of opium," since DTO is sometimes employed to abbreviate "diluted tincture of opium," which is a 1:25 dilution of opium tincture and water commonly employed to treat withdrawal symptoms in neonates. Further, paregoric's synonym "camphorated tincture of opium" should not be used, since it could easily be confused with "tincture of opium" or "deodorized tincture of opium."

The usual adult dosage of laudanum for the treatment of diarrhea is 0.6 mL (equivalent to 6 mg of morphine) four times a day. There is no maximum dose; refractory cases (e.g., diarrhea associated with AIDS) may require doses as high as 4 mL (equivalent to 40 mg of morphine) every three hours.

Methadone



Systematic (IUPAC) name

6-dimethylamino-4,4-diphenyl-heptan-3-one

Identifiers

CAS number 76-99-3

ATC code N02**AC52** N07**BC02**, R05**DA06**

PubChem 4095

DrugBank APRD00485

Chemical data

Formula $C_{21}H_{27}NO$

Mol. weight 309.445 g/mol

Pharmacokinetic data

Bioavailability **40-80(-92)**

Metabolism Hepatic

Half life 24-36 hrs.

Excretion Urine, Test by specific gravity and bilirubin

Therapeutic considerations

Pregnancy cat. Reduction of oxygen to unborn child due to depression of breathing

Legal status Class A(UK) Schedule II(US)

Dependence Liability Moderate

Routes oral, intravenous

Methadone is a synthetic opioid, used medically as an analgesic and in the treatment of narcotic addiction. It was first brought to market by the pharmaceutical company Eli Lilly and Company.

History

Methadone/dolophine, was first synthesized in 1937 by German scientists Max Bockmühl and Gustav Ehrhart at IG Farben (Hoechst-Am-Main) during their search for an analgesic that would be easier to use during surgery (and less potentially addictive, post-op) than morphine. Methadone is a Schedule II drug under the Single Convention on Narcotic Drugs[1].

On September 11, 1941 Bockmühl and Ehrhart filed an application for a patent for a synthetic substance they called Hoechst 10820 or polamidon and whose structure had no relation to morphine or the opioid alkaloids (Bockmühl and Ehrhart, 1949). Although chemically unlike morphine or heroin, methadone also acts on the opioid receptors and thus produces many of the same effects. Chemically, methadone is the simplest of the opioids.

Methadone was introduced into the United States in 1947 by Eli Lilly and Company as an analgesic (They gave it the trade name Dolophine,® which is now registered to Roxane Laboratories). Since then, it has been best known for its use in treating narcotic addiction, though it is also used in managing chronic pain due to its long duration of action and very low cost. In late 2004, the cost of a one-month supply of methadone was $20, as compared to an equivalent analgesic amount of Demerol at $120. The old name Dolophine comes from the German Dolphium. The name derives from the Latin dolor which means "pain" and phine which means "end".

Methadone (as Dolophine) was first manufactured in the USA by Mallinckrodt pharmaceuticals, a St. Louis-based subsidiary of the Tyco International corporation. Mallinckrodt held the patent up until the early 1990s. Today a number of pharmaceutical companies produce and distribute methadone. However, the major producer remains

Mallinckrodt. Mallinckrodt sells bulk methadone to most of the producers of generic preparations and also distributes its own brand name product in the form of tablets, dispersable tablets and oral concentrate under the name Methadose in the United States.

Generally, one will only hear "dolophine" used by older addicts who used the product in the 1960s and 1970s. Medical professionals who believe that dolophine is the generic name for methadone, when actually it is the reverse, may also use the old brand name. A persistent but untrue urban legend claims that the trade name "Dolophine" was coined in tribute to Adolf Hitler by its German creators, and it is sometimes even claimed that the drug was originally named "adolphine" or "adolophine". The claim is still presented as fact by Church of Scientology literature [2] and was repeated by actor and vocal Scientologist Tom Cruise in a 2005 Entertainment Weekly interview. However, as the magazine pointed out, this isn't true: the name "Dolophine" was in fact created after the war by the American branch of Eli Lilly [3], and the name "Adolphine" (never an actual name of the drug) was created in the United States in the early 1970s.[4]

Pharmacology

Methadone has a slow metabolism and very high lipid solubility, making it longer lasting than morphine-based drugs. Methadone has a typical half-life of 24-36 hours, permitting the administration only once a day in heroin detoxification and maintenance programs. The analgesic activity is shorter than the pharmacological halflife; dosing for pain control usually requires multiple doses per day. The most common mode of delivery at a methadone clinic is in an oral solution. Methadone is almost as effective when administered orally as by injection. As with heroin, tolerance and dependence usually develop with repeated doses. Tolerance to the different physiological effects of methadone varies. Tolerance to analgesia usually occurs during the first few weeks of use; whereas with respiratory depression, sedation, and nausea it is seen within approximately 5-7 days. There is no tolerance formed to constipation produced by methadone or other opioids, however, effects may be less severe after time.

Current research shows methadone has a unique affinity for the NMDA (N-methyl-D-aspartic acid) brain receptor. Some researchers propose that NMDA may regulate psychic dependence and tolerance by exhibiting opioid antagonist-like activity. Withdrawal symptoms are generally less acutely severe than those of morphine and heroin at equivalent doses, but are significantly more prolonged: it can last for weeks.

Clinical use

Opioid addiction

Methadone has traditionally been provided to the addiction population in a highly regulated methadone clinic, generally associated with an outpatient department of a hospital. Clinics such as these stem from programs set up during the Nixon administration to combat heroin use, first in Washington, D.C., then nationwide. In addition to obtaining a daily methadone dose, some who go to this type of clinic for addiction treatment may attend

some type of psychological counseling for their addiction. Some are required to attend drug addiction programs but many are not.

Methadone is considered to be generally effective in management of heroin addiction and reduction of HIV rates from needle sharing. At proper dosing, methadone usually reduces the appetite for and need to take heroin. However, some heroin addicts report more difficulty in quitting methadone than heroin. While there is much debate over the treatment schedule and duration required, treatment at a methadone maintenance clinic is intended to be for an indefinite duration. Many factors determine the treatment dose schedule, and some follow the philosophy that methadone maintenance treatment is not curative for heroin addiction.

Chronic pain

In recent years, methadone has gained popularity among physicians for the treatment of other medical problems, such as chronic pain. The increased usage comes as doctors search for an opioid drug that can be dosed less frequently than short-acting drugs like morphine or hydrocodone. Another factor in the increased usage is the low cost of methadone. A month's supply will typically have a retail cost of $30-50 in the United States, compared to hundreds of dollars for alternative opioids. Methadone, with its long half-life (and thus long duration of effect) and good oral bioavailability, is a common second-choice drug for pain that doesn't respond to weaker agonists. Some physicians also choose methadone for treating chronic pain in patients who are thought to have a propensity for addiction.

Methadone prescribed for chronic pain is also tied to an increasing number of drug overdose deaths in the United States, more than any other prescription narcotic painkiller.

According to the National Center for Health Statistics, as well as a 2006 series in the Charleston (WV) Gazette[5], medical examiners listed methadone as contributing to 2,992 deaths in 2003, up from 790 in 1999. Approximately 82% of those deaths were listed as accidental- and most deaths involved combinations of methadone with other drugs (especially benzodiazepines).

Data confirms a correlation between increased methadone distribution through pharmacy channels and the rise in methadone associated mortality. This supports the hypothesis that the growing use of oral methadone, prescribed and dispensed for the outpatient management of chronic pain (vs. opioid addiction treatment), explains the dramatic increases in methadone consumption and the growing availability of the drug for diversion to abuse.

More information on methadone associated mortality can be found at Substance Abuse and Mental Health Services Administration (SAMHSA - U.S. Dept. of Health and Human Services).

Efficacy

The efficacy of methadone, whether for heroin addiction or chronic pain, has long been debated. Methadone is a strong opiate that induces analgesia which is indistinguishable from morphine's and other opiate agonists. Regarding addiction, a Cochrane review (neutral organization that examines medical treatments) from 2004 noted, "Methadone is an effective

maintenance therapy intervention for the treatment of heroin dependence as it retains patients in treatment and decreases heroin use better than treatments that do not utilise opioid replacement therapy. It does not show statistically significant superior effect on criminal activity." In other words, opiate-dependent patients stayed in methadone programs, but reduction in criminal activity was no greater than that seen in patients treated without methadone. Of course, given the many clients of methadone programs who cease using drugs and live functional lives, the prescription of methadone seems to inarguably lead to a reduction in crime. These studies of criminal activity, however, ignore the many homeless and extremely impoverished who are in methadone programs. Such people cannot cease criminal activity because it is necessary, at least in the circumstances which they are currently in, to remain alive on a day to day basis. In studies of people with access to housing and jobs, the cessation of illegal opiate use (and continuance of legal opiate use) which methadone's prescription provides reduces criminality. In methadone users who continue to use other drugs and who have access to housing and jobs, the problem lies in use of non-opiate drugs. Since methadone use is not a substitute for non-opiate use, this is to be expected.

Worldwide, there has been an explosion of deaths related to methadone. At the same time, there has been a reduction of deaths due to other opiates. This is because methadone prescriptions have increased and other opiate prescriptions have decreased. Methadone has recently come into favor because of its morpine-equivalent analgesia and the longer half-life of methadone which makes blood levels and thus analgesia more stable in patients. Germany noted that one-half of its drug-related deaths were caused in whole or in part by methadone. In 1996, more than twice as many people died from methadone as died from heroin in England. It should be noted that most overdose deaths involving methadone were caused by concurrent use of benzodiazepines or other sedative drugs such as alcohol. Since the increase in deaths due to methadone has not been part of an increase in overall opiate agonist related deaths, it seems that the reason for this increase is simply a trend towards prescribing methadone rather than other opiates. Thus, scare tactics surrounding a upswing in methadone use and deaths are misleading: opiate use always exists. The particular opiate used matters little or not at all. Methadone, heroin, morphine, oxycodone, and others all have nearly identical effects, at least according to users. Thus, when the deaths to one increase the deaths due to another decrease. The amount of users remains stable while the actual opiate in use changes according to availability.

Abuse

Most methadone abuse is perpetrated by friends and family members of people who receive the drug on a prescription basis for medical conditions. "Street Methadone" has a black market value of roughly one U.S. Dollar per Milligram.

Although not common, methadone is encountered on the illicit drug market and has been associated with a number of overdose deaths. "Street Meth" demand comes primarily from opioid addicts unable to get into a legal methadone program, or addicts who have been removed from a methadone program due to some infraction. Methadone is not a common drug of choice because, generally speaking, addicts seeking a high strongly prefer shorter-acting opioids. Studies have shown that the vast majority of methadone diverted to the illicit

market comes from pain management prescriptions or theft from factories/shippers and not from maintenance patients.

Similar drugs

Closely related to methadone, the synthetic compound levo-alphacetylmethadol or LAAM (ORLAAM) has an even longer duration of action (from 48 to 72 hours), permitting a reduction in frequency of use. In 1994 it was approved as a treatment of narcotic addiction. Like methadone, LAAM is in Schedule II of the United States Controlled Substances Act. LAAM has since been removed from the US and European markets due to reports of rare cardiac side effects.

Buprenorphine has also been used in the treatment of narcotic addiction. In the UK and many other countries, however, not only buprenorphine and methadone but also diamorphine (heroin) and other opioids may be used for outpatient treatment of opiate addiction, and treatment is generally provided in much less heavily regulated environments than in the United States. A study from Austria indicated that oral morphine provides better results than oral methadone, and studies of heroin maintenance have indicated that a low background dose of methadone combined with heroin maintenance may significantly improve outcomes for less-responsive patients.

Another close relative of methadone is dextropropoxyphene, first marketed in 1957 under the trade name of Darvon. Oral analgesic potency is one-half to one-third that of codeine, with 65 mg approximately equivalent to about 600 mg of aspirin. Dextropropoxyphene is prescribed for relief of mild to moderate pain. Bulk dextropropoxyphene is in Schedule II of the United States Controlled Substances Act, while preparations containing it are in Schedule IV. More than 100 tons of dextropropoxyphene are produced in the United States annually, and more than 25 million prescriptions are written for the products. This narcotic is associated with a number of toxic side effects and is among the top 10 drugs reported by medical examiners in recreational drug use deaths.

Notes

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2. ^ Buttnor, Al. "The Drug Problem: How It CAN be Solved". Freedom Magazine (vol. 4, iss. 1) p. 15. Retrieved Apr. 7, 2006.

3. ^ http://www.exchangesupplies.org/publications/methadone_briefing/section1.html

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Narcotic

A *narcotic* is an addictive drug, derived from opium, that reduces pain, induces sleep and may alter mood or behavior. The derivation of the word is from the Greek word narkotikos, meaning "benumbing or deadening," and originally referred to a variety of substances that induce sleep (such state is *narcosis*).

In U.S. legal context, narcotic refers to opium, opium derivatives, and their semi-synthetic or fully synthetic substitutes as well as cocaine and coca leaves, which although classified as "narcotics" in the U.S. Controlled Substances Act (CSA), are chemically not narcotics.

Many law enforcement officials in the United States use the word 'narcotic' to refer to any illegal drug or any unlawfully possessed drug. An example is referring to cannabis as a narcotic. Because the term is often used broadly, inaccurately or pejoratively outside medical contexts, most medical professionals prefer the more precise term opioid, which refers to all natural, semi-synthetic and synthetic substances that behave pharmacologically like morphine, the primary active constituent of natural opium poppy.

Administration

Narcotics can be administered in a variety of ways. Some are taken orally, transdermally (skin patches) or injected. As recreational drugs, they are often smoked, snorted, or self-administered by the more direct routes of subcutaneous ("skin popping") and intravenous ("mainlining") injection.

Effects

Drug effects depend heavily on the dose, route of administration, previous exposure to the drug, and the expectation of the user. Aside from their clinical use in the treatment of pain, cough suppression and acute diarrhea, narcotics produce a general sense of well-being known as euphoria by reducing tension, anxiety, and aggression. These effects are helpful in a therapeutic setting and contribute to their popularity as recreational drugs, as well as helping to produce dependency.

Narcotic use is associated with a variety of effects including drowsiness, itching, sleeplessness, inability to concentrate, apathy, lessened physical activity, constriction of the pupils, dilation of the subcutaneous blood vessels causing flushing of the face and neck, constipation, nausea, vomiting and, most significantly, respiratory depression. As the dose is increased, the subjective, analgesic, and toxic effects become more pronounced. Except in cases of acute intoxication, there is no loss of motor coordination or slurred speech as occurs with many depressants such as alcohol or barbiturates.

Hazards

Among the hazards of careless or excessive drug use are the increasing risk of infection, disease and overdose. Medical complications common among recreational narcotic users

arise primarily from the non-sterile practices of injecting. Skin, lung and brain abscesses, endocarditis, hepatitis and HIV/AIDS are commonly found among persons with narcotic dependencies who share syringes or inhale the drug. There has been much discussion about the dangers related to the adulterants/diluents found in street drugs, such as heroin, where rumours abound about what is used to "cut" street drugs, e.g., ground glass, talcum powder, rat poison, domestic cleaning powders, and other cutting agents. Recent evidence shows that this kind of "dangerous adulteration" is largely mythical and that far less cutting of drugs than is normally assumed actually takes place. However, since there is no simple way to determine the purity of a drug that is sold on the street, the effects of using street narcotics are unpredictable. It remains the case that the greatest risk presented by most illicit drugs relates to the drugs themselves and how they are used, e.g., in conjunction with other drugs (alcohol is a particularly risky drug to use whilst also using other street drugs), in excess (most recreational and non-excessive drug use does not result in harm), and how a drug is administered (such as the sharing of needles). HIV and hepatitis infection rates drop among opioid injectors who have access to clean syringes and take advantage of that provision.

Tolerance and dependence

With repeated use of narcotics, tolerance and dependence develop. The development of tolerance is characterized by a shortened duration and a decreased intensity of analgesia, euphoria and sedation, which creates the need to administer progressively larger doses to attain the desired effect. Tolerance does not develop uniformly for all actions of these drugs, giving rise to a number of toxic effects. Although the lethal dose is increased significantly in tolerant users, there is always a dose at which death can occur from respiratory depression. It is clear, however, that tolerance and dependence, both part of the conventional idea of addiction, are insufficient to explain in totality what addiction is. Addiction proper is a broader behavioural phenomena that also encapsulates nonsubstance based activity that has many of the same characteristics that substance based dependency displays, e.g., excessive and compulsive gambling, excessive and compulsive eating, and a range of other excessive and compulsive behaviours. Moreover, it isn't always the case that those with a physical dependency to opiates find it too difficult to get over their "addiction," because so-called medical addicts (those that become physically dependent on opiates given for pain relief after treatment) only have to "give-up" the physical symptoms - they don't also have the all important psychological and life-style attachment to the drug which goes to make up the all-encompassing "addiction."

Physical dependence refers to an alteration of normal body functions that necessitates the continued presence of a drug in order to prevent the withdrawal or abstinence syndrome. The intensity and character of the physical symptoms experienced during withdrawal are directly related to the particular drug in use, the total daily dose, the interval between doses, the duration of use and the health and personality of the user. In general, narcotics with shorter durations of action tend to produce shorter, more intense withdrawal symptoms, while drugs that produce longer narcotic effects have prolonged symptoms that tend to be less severe.

The withdrawal symptoms experienced from opiod addiction are usually first felt shortly before the time of the next scheduled dose. Early symptoms include watery eyes, runny nose,

yawning and sweating. Restlessness, irritability, loss of appetite, tremors and severe sneezing appear as the syndrome progresses. Severe depression and vomiting are not uncommon. The heart rate and blood pressure are elevated. Chills alternating with flushing and excessive sweating are also characteristic symptoms. Pains in the bones and muscles of the back and extremities occur as do muscle spasms and kicking movements, which may be the source of the expression "kicking the habit." At any point during this process, a suitable dose of any opioid can be administered that will dramatically reverse the withdrawal symptoms. Without intervention, the syndrome will run its course and most of the overt physical symptoms will disappear within 5 to 15 days, depending on the opiod used.

The psychological dependence that is associated with narcotic addiction is complex and protracted. Long after the physical need for the drug has passed, the addict may continue to think and talk about the use of drugs. There is a high probability that relapse will occur after narcotic withdrawal when neither the physical environment nor the behavioral motivators that contributed to the abuse have been altered.

There are two major patterns of narcotic dependence seen in the United States. One involves individuals whose drug use was initiated within the context of medical treatment who escalate their dose through "doctor shopping" or branch out to illicit drugs. A very small percentage of addicts are in this group.

The other more common pattern of non-medical use is initiated outside the therapeutic setting with experimental or recreational use of narcotics. The majority of individuals in this category may use narcotics sporadically for months or even years. These occasional users are called "chippers." Although they are neither tolerant of nor dependent on narcotics, the social, medical and legal consequences of their behavior can be very serious. Some experimental users will escalate their narcotic use and will eventually become dependent, both physically and psychologically. The earlier drug use begins, the more likely it is to progress to dependence. Heroin use among males in inner cities is generally initiated in adolescence, and dependence often develops in about 1 or 2 years.

Signs and symptoms of narcotic/opioid *overdose* include the following: euphoria, arousable somnolence ("nodding"), nausea, pinpoint pupils (except with Pethidine/Meperidine [Demerol]), hypoxia, or in combination with other types of drugs, coma, and seizures.

See also

- Hard and soft drugs

Opium

Opium, or *opïum* is a narcotic analgesic drug which is obtained from the unripe seed pods of the opium poppy (Papaver somniferum L. or the synonym paeoniflorum).

Harvesting opium

To harvest opium, the skin of the ripening pods is scored by a sharp blade. The slashes exude a white, milky latex, which dries to a sticky brown resin that is scraped off the pods as raw opium.

Opium has powerful narcotic properties. Its constituents and derivatives are used as painkillers. Therefore, legal opium production is allowed under the United Nations Single Convention on Narcotic Drugs and other international drug treaties, subject to strict supervision by the law enforcement agencies of individual countries. The leading legal producer of opium is India, which is also the only place on earth where opium is still legally harvested by the traditional method of incising the pods. Other important national cultivators of opium poppies for the pharmaceutical industry are Tasmania in Australia, and France. Several other countries cultivate the poppy to satisfy the demand of their domestic pharmaceutical companies, but not for export. However, it is not strictly true to say that these nations produce opium. They cultivate Papaver somniferum, but the alkaloids are collected via the Gregory process, whereby the entire poppy, excluding roots and leaves, is mashed and stewed in dilute acid solutions. The alkaloids are then recovered via Acid/Base extraction and purified. This process was developed in the UK during World War II, when wartime shortages of many essential drugs encouraged innovation in pharmaceutical processing. The French company Francopia produces 20% to 25% of the world's total requirement for legal opioids, with total sales of approximately €60 million. The UN treaty requires that every country submit annual reports to the International Narcotics Control Board, stating that year's actual consumption of many classes of controlled drugs as well as opioids, and projecting required quantities for the next year. This is to allow trends in consumption to be monitored, and production quotas allotted. The market for export of controlled drugs is fixed by regulation, in part due to the discovery in the 1930's that huge amounts of opioids had been diverted from the legal pharmaceutical market to the black market via a complex web of front companies and forged declarations. The main participants at that time were Swiss pharmaceutical producers and brokers, and the military regime in pre-World War 2 Japan, who claimed to be consuming thousands of tonnes of opium, morphine and heroin. The products were in fact transported to China, where opium was directly used as part of the Japanese policy of annexation of Manchuria, and other aggression against China.

A recent proposal from the European Senlis Council hopes to solve the problems caused by the massive quantity of opium produced illegally in Afghanistan, most of which is converted to heroin, and smuggled for sale in Europe and the USA. This proposal is to licence Afghan farmers to produce opium for the world pharmaceutical market, and thereby solve another problem, that of chronic underuse of potent analgesics where required within developing nations. In the industrialised world the USA is the world's biggest consumer of prescription opioids, with Italy one of the lowest. The Italian medical profession seems to have recently accepted that opioids have applications apart from pain relief in terminal cancer. Recorded Italian consumption has increased considerably of late.

To this end Senlis arranged a conference in Kabul, to discuss the idea, but it remains to be seen if this will happen; internal security and corruption issues within Afghanistan make it unlikely that they soon will be able to meet the stringent UN requirements for legal production of opioids for export. If the record of CIA interference with attempts to "buy and

burn" illicit Burmese opium harvests in the past is considered (McCoy, 1991), Afghanistan's opium may be a major part of current War on Drugs policies for some time.

Opium preparation

Raw opium must be processed and refined (called "cooking") before it is suitable for smoking. The raw opium is first dissolved in water and simmered over a low heat. The brown solution is then filtered to remove the vegetable matter, soil, insect material, and other contaminants along with the polysacharrides, lipids and waxes that are components of the poppy pod. The filtrate is then evaporated slowly over a low heat. The result is a smokable form of opium with a considerably higher morphine content percentage-wise than the raw latex. This is then pressed into bricks and either transported to heroin laboratories or used as is.

The smoking of opium does not involve the pyrolysis of the material as might be imagined. Rather the prepared opium is indirectly heated to temperatures at which the active alkaloids, chiefly morphine, are vaporized. In the past smokers would lie down with specially designed pipes which had long stems and a metallic receptacle. A small amount of opium up to the size of a pea would be placed in the receptacle and the material heated indirectly by means of a candle or lamp. The smoker would lie on his or her side and inhale the vaporized morphine as needed. The pipe was commonly designed in a rounded cross section, so as to enable the metallic receptacle to be rotated into the heat source and then rest back upright as required. The pea sized material could be sufficient for up to an hour of intermittent use.

Opium is more traditionally used in the form of paregoric to treat diarrhea. It was also used in the form of laudanum, an alcoholic tincture which was commonly used as a pain medication. Samuel Taylor Coleridge is famously known to have composed his incomplete poem Kubla Khan while intoxicated with laudanum.

Most opium imported into the United States is broken down into its alkaloid constituents. These alkaloids are divided into two distinct chemical classes, phenanthrenes and isoquinolines. The principal phenanthrenes are morphine, codeine, and thebaine, while the isoquinolines have no significant central nervous system effects and are not regulated under the Controlled Substances Act. Opium is also processed into heroin, and most current drug use occurs with processed derivatives rather than with raw opium.

Seed capsules

The seed capsules also contain morphine, codeine, and other alkaloids. These pods can be steeped in water to produce a bitter tea that induces a long-lasting intoxication.

Chemical properties and physiological effects

Opium resin contains two groups of alkaloids: phenanthrenes (including morphine and codeine) and benzylisoquinolines (including papaverine). Morphine is by far the most prevalent and important alkaloid in opium, consisting of 10%-16% of the total. It binds to and activates ¼-opioid receptors in the brain, spinal cord, stomach and intestine. Regular

use leads to physical tolerance and possibly dependence. Various degrees of psychological addiction can occur, though this is relatively rare when opioids are used for treatment of pain, rather than for euphoric effects. These mechanisms result from changes in nervous system receptors in response to the drug. In response to the drug, the brain creates new receptors for opioids. These receptors are "pseudo" receptors and do not work. When the opioids are out of the body, the brain has the same amount of endogenous opioid (endorphins) to fill these receptors, but less of the functional receptors and more non-functional ones. Abstaining from the drug for a time allows the brain to replace the pseudo receptors with functioning ones (a gradual process).

Production today

Since being largely outlawed, the production of opium has significantly decreased around the world, despite an increasing demand. Opium is still being produced today legally for medicine. Afghanistan is currently the number one producer of the drug. During Taliban rule, the production of opium significantly decreased to 74 metric tons per year, but after the toppling of the Taliban by the Northern Alliance with foreign support in 2001, production has increased again. Opium exports make up a very large portion of Afghanistan's GDP, alongside natural gas and agriculture. According to DEA statistics, Afghanistan's production of oven-dried opium increased to 1,278 metric tons in 2002 shortly after the U.S. led invasion. Recent DEA statistics say that production more than doubled by 2003, and nearly doubled again during 2004. The UN Office on Drugs and Crime predicted a 6,100 tonne harvest of opium in year 2006 alone, and considers Afghanistan accountable for 92% [2] of the world's opium supply. In late 2004, the CIA estimated that 206,000 hectares were under poppy cultivation and that the new crop would generate 7 billion dollars worth of heroin. "There is no other country in the world that has 206,000 hectares under cultivation of any drug," said King Charles.

Besides Afghanistan, smaller quantities of opium are produced in Pakistan, the Golden Triangle region of Southeast Asia (particularly Myanmar), Colombia and Mexico. Opium is typically not transported and sold raw. Instead, specialized chemical factories are used to convert it into heroin - a much more potent and compact form of the drug.

History of opium

Ancient usage

The image of the poppy capsule was an attribute of deities, long before opium was extracted from its milky latex. At the Metropolitan Museum's Assyrian relief gallery, a winged deity in a bas-relief from the palace of Ashurnasirpal II at Nimrud, dedicated in 879 BC, bears a bouquet of poppy capsules on long stems, described by the museum as "pomegranates".

Modern usage

Until the practice of smoking was introduced to Europe and Asia after tobacco smoking in the Americas was observed and copied, opium was mostly either eaten or drunk. An early form of opium smoking involved the consumption of madak, a blend of tobacco and opium that became common in Asia in the 17th and 18th centuries. By the 19th century, in part because of a ban on madak in China, smoking of pure opium became more common. By this time, opium use had become widespread across much of the world, although consumption patterns and routes of administration varied.

Beginning with territorial conquest in India (in 1757), the British East India Company pursued a monopoly on opium production and export in India. This was met with varying degrees of success, but had a serious impact on the peasant cultivators (ryots) who were

often coerced or offered cash advances on their crops to encourage cultivation. This was something that was not done for any other crops, save for indigo. The product was sold by the chest in auctions in Calcutta and then smuggled into China. The East India Company used the profit to purchase teas which was in high demand in Britain.

Due to the growing British demand for Chinese tea, and the Chinese refusal to accept payment other than silver bullion, the British sought to substitute another commodity for which China was not self sufficient to alleviate the silver drain, which was beginning to cause a burden on the British economy. Opium was sucessfully used by the British traders to replace silver in exchange for Chinese tea for a period of decades. Many Chinese became addicted to opium, wreaking havoc among much of China's population. In response, the Imperial Qin dynasty halted the import of opium, demanding silver be traded instead. This response led to the Opium Wars, the British not willing to replace the cheap opium with costly silver. The first opium war led to Britain seizing Hong Kong and to what the Chinese term the "century of shame". This illegal trade became one of the world's most valuable single commodity trades and was described by the eminent Harvard University historian John K. Fairbank as a heroin. Many large American fortunes were built in the opium trade, including those of John Jacob Astor (partially and briefly), John Kerry (from his Forbes grandfather), and Franklin Delano Roosevelt (from his Delano grandfather). Thomas De Quincey's Confessions of an English Opium-Eater is one of the first literary accounts of opium addiction written from the point of view of an addict, in the early 1820s. Later, Opium smoking became associated with immigrant Chinese communities around the world, with "opium dens" becoming notorious fixtures of many Chinatowns.

Modern prohibition

There were no legal restrictions on the importation or use of opium in the United States until a San Francisco, California ordinance which banned the smoking of opium in opium dens in 1875. The Opium Exclusion Act of 1909 prohibited its importation. Other important legislation included the Harrison Narcotics Tax Act of 1914. Before this time, medicines often contained opium without any warning label. U.S president William Henry Harrison was treated with opium in 1841. Countless miracle cures contained opium, which of course was the reason many of these were so successful, since people started taking these cures because they made them feel good. Opium was even touted as an alcoholism cure, evidently to the wives of alcoholics. This would be because an opium addict, capable of supporting his habit on about 5 cents a day, would likely be a more suitable companion for a wife—being placid and calm, mostly—than an alcoholic husband. Today, there are numerous national and international laws governing the production and distribution of narcotic substances. In particular, Article 23 of the Single Convention on Narcotic Drugs requires opium-producing nations to designate a government agency to take physical possession of licit opium crops as soon as possible after harvest and conduct all wholesaling and exporting through that agency. Opium's pharmaceutical use is strictly controlled worldwide and non-pharmaceutical uses are generally prohibited.

Opium poppies are popular and attractive garden plants, whose flowers vary greatly in colour, size and form. A modest amount of domestic cultivation in private gardens is not

usually subject to legal controls. The dried seed cases are often used for decorations, and the small seeds themselves—which contain negligible amounts of any opioid alkaloids—are a common and flavoursome topping for breads and cakes.

Medicinal uses

Opium has been a major item of trade for centuries, and has long been used as a painkiller and sedative. It was well known to the Ancient Macedonians, who named it opium (opi = drunken, um = mind). Many patent medicines of the 19th century were based around laudanum (known as "tincture of opium", a solution of opium in ethyl alcohol). As a result of this substance being branded a miracle cure for many common illnesses (ranging from colds to alcoholism), the substance developed a very large number of addicts at the time. Fortunately for these addicts, they did not lose their jobs or much of their respectability as a result of this, and an opium addiction was considered more similar to a gambling or alcohol addiction. Also, since a man could remain an opium addict on 5 cents a day, it did not cause undue financial strain, and therefore no damage to the person was caused that one living under an 'addict' lifestyle in the modern sense would risk suffering. Tincture of opium is prescribed in modern times, among other reasons, for ongoing, severe diarrhea caused, for example, by the creation of an ileostomy. A 10% tincture of opium solution (10% opium, 90% ethyl alcohol) taken 30 minutes prior to meals will significantly slow intestinal motility, giving the intestines greater time to absorb fluid in the stool.

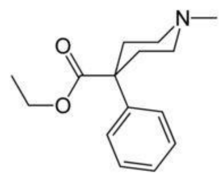
Literature

There is a rich and longstanding literature by and about opium users. Perhaps the most famous work of this kind is Thomas De Quincey's Confessions of an English Opium Eater, a work which details both the pleasures and the dangers of the drug. Other works from nineteenth century Britain include "The Lotos-Eaters" by Alfred Lord Tennyson and (some would argue) Goblin Market by Christina Rossetti, which depicts thinly-veiled experiences of addiction and withdrawal. Samuel Taylor Coleridge's poem "Kubla Khan" is also widely considered to be a poem of the opium experience. In the twentieth century Aldous Huxley wrote about the experience of opium. In 1957 the physician Douglas Hubble wrote an article called "Opium Addiction and English Literature" that chronicles the use of opium by prominent English writers, and its influence on their works [5]. The sleep-inducing properties of opium are presented in the book and subsequent movie, The Wonderful Wizard of Oz. At one point in the story, Dorothy and her friends are drawn by the wicked witch into a field of poppies, in which they fall asleep.

See also

- Opioid
- Psychoactive drug

Pethidine



Systematic (IUPAC) name

Ethyl-1-methyl-4-phenylpiperidine-4-carboxylate

Identifiers

CAS number 57-42-1

ATC code N02**AB02**

PubChem 4058

DrugBank APRD00074

Chemical data

Formula $C_{15}H_{21}NO_2$

Mol. weight 247.33

Pharmacokinetic data

Bioavailability **variable**

Protein binding 65-75%

Metabolism Liver

Half life 3-5 hours

Excretion Renal

Therapeutic considerations

Pregnancy cat. $C_{(AU)}$ $C_{(US)}$

Legal status S8(AU) Class A(UK) Schedule II(US)

Routes oral, IV, IM

Pethidine (INN) or *meperidine* (USAN) (also referred to as: isonipecaine; lidol; operidine; pethanol; piridosal; Algil®; Alodan®; Centralgin®; Demerol®; Dispadol®; Dolantin®; Dolargan® (in Poland)[1]; Dolestine®; Dolosal®; Dolsin®; Mefedina®) is a fast-acting opioid analgesic drug. In the United States, it is more commonly known as meperidine or by its brand name Demerol.

Pethidine is indicated for the treatment of moderate to severe pain, and is delivered as hydrochloride tablets, as a syrup, or by intramuscular or intravenous injection. For much of the 20th century, pethidine was the opioid of choice for many physicians. Compared to morphine, pethidine was supposed to be safer and carry less risk of addiction, and superior in treating the pain associated with biliary spasm or renal colic due to its putative antispasmodic effects. In fact, pethidine is no more effective than morphine at treating biliary or renal pain, and its low potency, short duration of action, and unique toxicity (i.e. seizures, delirium, other neuropsychological effects) relative to other available agents have seen it fall out of favor in recent years, for all but a very few, very specific indications. Nevertheless, some physicians continue to use it as a first-line strong opioid.

Mode of action

Main article: Opioid

Pethidine's efficacy as an analgesic was discovered fortuitously; it was synthesized in 1939 as an antimuscarinic agent. Pethidine exerts its analgesic effects by the same mechanism as morphine, by acting as an agonist at the ¼-opioid receptor. In addition to its strong opiodergic and anticholinergic effects, it has local anesthetic effects related to its interactions with sodium ion channels. Pethidine's in vitro efficacy as an "antispasmodic" is due to its local anesthetic effects. It does not, contrary to popular belief, have antispasmodic effects in vivo. It has also been associated with cases of serotonin syndrome, suggesting some interaction with serotonergic neurons, but the relationship has not been definitively demonstrated. It is more lipid-soluble than morphine, resulting in a faster onset of action. Its duration of clinical effect is 120-150 minutes. Like other opioid drugs, pethidine has the potential to be both physically and psychologically habituating. The especially severe side effects unique to pethidine among opioids are thought to be primarily due to the action of its metabolite, norpethidine.

Pharmacokinetics

Pethidine is quickly hydrolysed in the liver to pethidinic acid and is also demethylated to norpethidine, which has half the analgesic activity of pethidine but a longer elimination half-life (8-12 hours[2]); accumulating with regular administration, or in renal failure. Norpethidine is toxic and has convulsant and hallucinogenic effects. The toxic effects mediated by the metabolites cannot be countered with opioid receptor antagonists such as naloxone or naltrexone and are probably primarily due to norpethidine's anticholinergic activity; its pharmacology has not been thoroughly explored. The neurotoxicity of pethidine's metabolites is a unique feature of pethidine compared to other opioids.

Pethidine's metabolites are further conjugated with glucuronic acid and excreted into the urine.

Interactions

Pethidine has serious interactions that can be dangerous with MAOIs (e.g. furazolidone, isocarboxazid, linezolid, moclobemide, phenelzine, procarbazine, selegiline, tranylcypromine, naltrexone, ritonavir, and sibutramine). Such patients may suffer agitation, delirium, headache, convulsions, and/or hyperthermia. It is thought to be caused by an increase in cerebral serotonin concentrations. It is possible that Pethidine can also interact with a number of other medications, including muscle relaxants, some antidepressants, benzodiazepines, and alcohol.

Pethidine is also relatively contraindicated for use when a patient is suffering from liver, or kidney disease, has a history of seizures or epilepsy, has an enlarged prostate or urinary retention problems, or suffers from hyperthyroidism, asthma, or Addison's disease.

Adverse effects

Main article: Opioid

In addition to the adverse effects common to all opioids, such as constipation, dry mouth, lightheadedness, itchiness, muscular twitches, and nausea, the repeated administration of pethidine can lead to neurotoxic effects.

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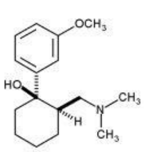
2. ^ Norpenthedine half-life. 2002. Australian prescriber[1]

Tramadol



Systematic (IUPAC) name

rac-(1R,2R)-2-(dimethylaminomethyl)-1-(3-methoxyphenyl)-cyclohexanol

Identifiers

CAS number 27203-92-5

ATC code N02**AX02**

PubChem 33741

DrugBank APRD00028

Chemical data

Formula $C_{16}H_{25}NO_2$

Mol. weight 263.4 g/mol

Pharmacokinetic data

Bioavailability 68-72% Increases with repeated dosing.

Protein binding 20%

Metabolism Hepatic demethylated & glucuronidated

Half life 5-7 hours

Excretion Renal

Therapeutic considerations

Pregnancy cat. $C_{(AU)}$ $C_{(US)}$

Legal status $S4_{(AU)}$ $POM_{(UK)}$

Routes oral, IV, IM

Tramadol (INN) (IPA: [ÈtræmYdRl]) is an atypical opioid which is a centrally acting analgesic, used for treating moderate to severe pain. It is a synthetic agent, unrelated to other opioids, and appears to have actions on the GABAergic, noradrenergic and serotonergic systems. Tramadol was developed by the German pharmaceutical company Grünenthal GmbH and marketed under the trade name *Tramal*. Grünenthal has also cross licensed the drug to many other pharmaceutical companies that market it under various names, some of which are listed below.

Tramadol is usually marketed as the hydrochloride salt (*tramadol hydrochloride*) and is available in both injectable (intravenous and/or intramuscular) and oral preparations (e.g. *Zydol*® in UK and *Ultram*® in US). It is also available in conjunction with paracetamol (acetaminophen) as *Ultracet*®.

Dosages vary depending on the degree of pain experienced by the patient. Tramadol is approximately 10% as potent as morphine, when given by the IV/IM route. Oral doses range from 50–400 mg daily, with up to 600 mg daily when given IV/IM.

Mechanism of action

The mode of action of tramadol has yet to be fully elucidated, but it is believed to work through modulation of the GABAergic, noradrenergic and serotonergic systems. The contribution of non-opioid activity is demonstrated by the analgesic effects of tramadol not being fully antagonised by the ¼-opioid receptor antagonist naloxone.

Tramadol is marketed as a racemic mixture with a weak affinity for the ¼-opioid receptor (approximately 1/6000th that of morphine). The (+)-enantiomer is approximately four times more potent than the (-)-enantiomer in terms of ¼-opioid receptor affinity and 5-HT reuptake, whereas the (-)-enantiomer is responsible for noradrenaline reuptake effects (Shipton, 2000). These actions appear to produce a synergistic analgesic effect, with (+)-tramadol exhibiting 10-fold higher analgesic activity than (-)-tramadol (Goeringer et al., 1997).

The serotonergic modulating properties of tramadol mean that it has the potential to interact with other serotonergic agents. There is an increased risk of serotonin syndrome when tramadol is taken in combination with serotonin reuptake inhibitors (e.g. SSRIs), since these agents not only potentiate the effect of 5-HT but also inhibit tramadol's metabolism.

It is suggested that tramadol could be effective for alleviating symptoms of depression and anxiety because of its action on GABAergic, noradrenergic and serotonergic systems. However, use of the drug for treatment of such disorders by a health professional is unlikely.

Tramadol may also be used to treat hypertension when other treatments have failed.

Metabolism

Tramadol undergoes hepatic metabolism via the cytochrome P450 isozyme CYP2D6, being O- and N-demethylated to 5 different metabolites. Of these, M1 is the most significant since it has 200 times the ¼-affinity of (+)-tramadol, and furthermore has an elimination half-life of 9 hours compared to 6 hours for tramadol itself. In the 6% of the population who have slow CYP2D6 activity, there is therefore a slightly reduced analgesic effect. Phase II hepatic metabolism renders the metabolites water-soluble and they are renally excreted. Thus reduced doses may be used in renal and hepatic impairment.

Adverse effects

The most commonly reported adverse drug reactions are nausea, vomiting and sweating. Drowsiness is reported, although it is less of an issue compared to other opioids. Respiratory depression, a common side effect of most opioids, is not clinically significant in normal doses. By itself, it does not decrease the seizure threshold, though it may do so if used in combination with SSRIs, tricyclic antidepressants, or in patients with epilepsy. A few seizures have been reported in humans receiving excessive single oral doses (700 mg) or large intravenous doses (300 mg).

Dependence

Some controversy exists regarding the dependence liability of tramadol. Grünenthal has promoted it as an opioid with a low risk of dependence compared to traditional opioids, claiming little evidence of such dependence in clinical trials. They offer the theory that since the M1 metabolite is the principal agonist at ¼-opioid receptors, the delayed agonist activity reduces dependence liability. The noradrenaline reuptake effects may also play a role in reducing dependence.

Despite these claims it is apparent, in community practice, that dependence to this agent does occur. This would be expected since analgesic and dependence effects are mediated by the same ¼-opioid receptor. However, this dependence liability is considered relatively low by health authorities, such that tramadol is classified as a Schedule 4 Prescription Only Medicine in Australia, rather than as a Schedule 8 Controlled Drug like other opioids (Rossi, 2004). Similarly, tramadol is not currently scheduled by the U.S. DEA, unlike other opioid analgesics. Nevertheless, the Prescribing Information for Ultram warns that tramadol "may induce psychological and physical dependence of the morphine-type."

Proprietary preparations

Grünenthal, which still owns the patent to tramadol, has cross-licensed the agent to various pharmaceutical companies internationally. Thus tramadol is marketed under many trade names including: Adolonta, Calmador, Contramal, Crispin, Lumidol, Mosepan, Nobligan, Siverol, Tiparol, Toplagic, Tradol, Tradolan, Tralgit, Tramacet, Tramacip, Tramadin, Tramal, Tramahexal, Tramazac, Tramedo, Ultracet, Ultram, Zamadol and Zydol.

Often used to treat

- Moderate pain
- Severe pain
- Most types of Neuralgia, including Trigeminal Neuralgia.
- Multiple other conditions that result in severe pain to the victim.
- Post operative pain in canines.

Trivia

- Rapper Russell Jones (a.k.a. Ol' Dirty Bastard) died from a combination of cocaine and a Tramadol overdose on November 13, 2004.

References

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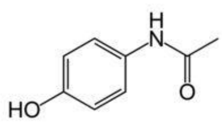
Paracetamol



Systematic (IUPAC) name

N-(4-hydroxyphenyl)acetamide

Identifiers

CAS number 103-90-2

ATC code N02**BE01**

PubChem 1983

DrugBank APRD00252

Chemical data

Formula $C_8H_9NO_2$

Mol. weight 151.17

Physical data

Density 1.263 g/cm^3

Melt. point 169 °C (336 °F)

Solubility in water 1.4g/100ml or .014 mg/mL (20 °C)

Pharmacokinetic data

Bioavailability **almost 100%**

Metabolism 90 to 95% hepatic

Half life 1–4 hours

Excretion renal

Therapeutic considerations

Pregnancy cat. $A_{(AU)}$ $B_{(US)}$

Legal status $S2_{(AU)}$ $GSL_{(UK)}$ $OTC_{(US)}$

Routes oral, rectal, IV

Paracetamol (INN) (IPA: [pærYÈsitYmRl, -moŠl, -Ès[tY-]) or *acetaminophen* (USAN), is a common analgesic and antipyretic drug that is used for the relief of fever, headaches, and other minor aches and pains. Paracetamol is also useful in managing more severe pain, allowing lower dosages of additional non-steroidal anti-inflammatory drugs (NSAIDs) or opioid analgesics to be used, thereby minimizing overall side-effects. It is a major ingredient in numerous cold and flu medications, as well as many prescription analgesics. It is remarkably safe for human use in recommended doses, but because of its wide availability, deliberate or accidental overdoses are fairly common.

Common brand names for the drug include *Herron* in Australia, *Tylenol* in Brazil, Canada, South Korea and the U.S., *Paralen* in the Czech Republic and Slovakia, *Panadol* in Central America, Australia, New Zealand, Pakistan, Malaysia, Hong Kong, the UK, Portugal and Singapore, *Perdolan* in Belgium, *Doliprane*, *Dafalgan*, and *Efferalgan* in France, *Tachipirina* and *Efferalgan* in Italy, *Crocin* in India, *Gelocatil* in Spain, *Benuron* in Portugal, *Alvedon* in Sweden, *Panodil* and *Pinex* in Denmark and Iceland, *Acamol* in Israel, *Pinex* and *Paracet* in Norway, *Depon* in Greece and *Lekadol* in Slovenia.

The words acetaminophen and paracetamol both come from the chemical names for the compound: N-*acet*yl-para-*aminophen*ol and *par*a-*acet*yl-*am*ino-phen*ol*. In some contexts, it is shortened to *apap*, for N-*a*cetyl-*p*ara-*a*mino*p*henol.

History

In ancient and medieval times, the only antipyretic agents known were compounds contained in white willow bark (a family of chemicals known as salicins, which led to the development of aspirin), and compounds contained in cinchona bark. Cinchona bark was also used to create the anti-malaria drug quinine. Quinine itself also has antipyretic effects. Efforts to refine and isolate salicin and salicylic acid took place throughout the middle- and late-19th century, and was accomplished by Bayer chemist Felix Hoffman (this was also done by French chemist Charles Gergardt 40 years earlier, but he abandoned the work after deciding it was too impractical).[1]

When the cinchona tree became scarce in the 1880s, people began to look for alternatives. Two alternative antipyretic agents were developed in the 1880s: Acetanilide in

1886 and Phenacetin in 1887. By this time, paracetamol had already been synthesized by Harmon Northrop Morse via the reduction of p-nitrophenol with tin in glacial acetic acid. While this was first performed in 1873, paracetamol was not used medically for another two decades. In 1893, paracetamol was discovered in the urine of individuals who had taken phenacetin, and was concentrated into a white, crystalline compound with a bitter taste. In 1899, paracetamol was found to be a metabolite of acetanilide. This discovery was largely ignored at the time.

In 1946, the Institute for the Study of Analgesic and Sedative Drugs awarded a grant to the New York City Department of Health to study the problems associated with analgesic agents. Bernard Brodie and Julius Axelrod were assigned to investigate why non-aspirin agents were associated with the development of methemoglobinemia, a condition that decreases the oxygen-carrying capacity of blood and is potentially lethal. In 1948, Brodie and Axelrod linked the use of acetanilide with methemoglobinemia and determined that the analgesic effect of acetanilide was due to its active metabolite paracetamol. They advocated the use of paracetamol (acetaminophen), since it did not have the toxic effects of acetanilide.[1]

The product went on sale in the United States in 1955 under the brand name Tylenol.

In 1956, 500 mg tablets of paracetamol went on sale in the United Kingdom under the trade name *Panadol*, produced by Frederick Stearns & Co, a subsidiary of Sterling Drug Inc. Panadol was originally available only by prescription, for the relief of pain and fever, and was advertised as being "gentle to the stomach," since other analgesic agents of the time contained aspirin, a known stomach irritant. In June 1958 a children's formulation, *Panadol Elixir*, was released.

In 1963, paracetamol was added to the British Pharmacopoeia, and has gained popularity since then as an analgesic agent with few side-effects and little interaction with other pharmaceutical agents.

The U.S. patent on paracetamol has expired and generic versions of the drug are widely available under the Drug Price Competition and Patent Term Restoration Act of 1984, although certain Tylenol preparations are protected until 2007. U.S. patent 6,126,967 filed September 3, 1998 was granted for "Extended release acetaminophen particles."

Available forms

Panadol, which is marketed in Europe, Asia, Central America, and Australasia, is the most widely available brand, sold in over 80 countries. In North America, paracetamol is sold in generic form (usually labelled as acetaminophen) or under a number of trade names: for instance *Tylenol* (McNeil-PPC, Inc), *Anacin-3*, *Tempra*, and *Datril*.

In some formulations paracetamol is combined with the opioid codeine, sometimes referred to as co-codamol (BAN). In the United States and Canada, this is marketed under the name of Tylenol #1/2/3/4 and in the U.S. is only available by prescription, while the lowest strength is over-the-counter in Canada. In the UK and in many other countries, this combination is marketed under the names of Tylex CD and Panadeine. Other names include Captin, Disprol, Dymadon, Fensum, Hedex, Mexalen, Nofedol, Paralen, Pediapirin, Perfalgan, and Solpadeine. Paracetamol is also combined with other opioids such as dihydrocodeine, referred to as co-dydramol (BAN), oxycodone or hydrocodone, marketed in the U.S. as

Percocet and Vicodin, respectively. Another very commonly used analgesic combination includes acetaminophen in combination with propoxyphene napsylate, sold under the brand name Darvocet. A combination of paracetamol, codeine, and the calmative doxylamine succinate is marketed as Syndol or Mersyndol.

Acetaminophen is commonly used in multi-ingredient preparations for migraine headache, typically including butalbital and acetaminophen with or without caffeine, and sometimes containing codeine. In the U.S., these anti-migraine products are marketed under the brand name Fioricet.

It is commonly administered in tablet, liquid suspension, suppository or intravenous form. The common adult dose is 500 mg to 1000 mg. The recommended maximum daily dose, for adults, is 4 grams. In recommended doses paracetamol is safe for children and infants as well as for adults.

The effectiveness of paracetamol is often underestimated because of its widespread availability.

Mechanism of action

Paracetamol has long been suspected of having a similar mechanism of action to aspirin because of the similarity in structure. That is, it has been assumed that paracetamol acts by reducing production of prostaglandins, which are involved in the pain and fever processes, by inhibiting the cyclooxygenase (COX) enzyme.

However, there are important differences between the effects of aspirin and those of paracetamol. Prostaglandins participate in the inflammatory response which is why it has been known to trigger symptoms in asthmatics, but paracetamol has no appreciable anti-inflammatory action and hence does not have this side-effect. Furthermore, COX also produces thromboxanes, which aid in blood clotting — aspirin reduces blood clotting, but paracetamol does not. Finally, aspirin and the other NSAIDs commonly have detrimental effects on the stomach lining, where prostaglandins serve a protective role, but paracetamol is safe.

Indeed, while aspirin acts as an irreversible inhibitor of COX and directly blocks the enzyme's active site, paracetamol indirectly blocks COX, and that this blockade is ineffective in the presence of peroxides.[2] This might explain why paracetamol is effective in the central nervous system and in endothelial cells but not in platelets and immune cells which have high levels of peroxides.

In 2002 it was reported that paracetamol selectively blocks a variant of the COX enzyme that was different from the then known variants COX-1 and COX-2.[3] This enzyme, which is only expressed in the brain and the spinal cord, is now referred to as COX-3. Its exact mechanism of action is still poorly understood, but future research may provide further insight into how it works.

A single study has shown that administration of paracetamol increases the bioavailability of serotonin (5-HT) in rats,[4] but the mechanism is unknown and untested in humans.

Metabolism

Paracetamol is metabolized primarily in the liver, where most of it (60-90% of a therapeutic dose) is converted to inactive compounds by conjugation with sulfate and glucuronide, and then excreted by the kidneys. Only a small portion (5-10% of a therapeutic dose) is metabolized via the hepatic cytochrome P450 enzyme system (specifically CYP2E1); the toxic effects of paracetamol are due to a minor alkylating metabolite (N-acetyl-p-benzo-quinone imine, abbreviated as NAPQI) that is produced through this enzyme, not paracetamol itself or any of the major metabolites. The metabolism of paracetamol is an excellent example of toxication, because the metabolite NAPQI is primarily responsible for toxicity rather than paracetamol itself.

At usual doses, the toxic metabolite NAPQI is quickly detoxified by combining irreversibly with the sulfhydryl groups of glutathione to produce a non-toxic conjugate that is eventually excreted by the kidneys.

Comparison with NSAIDs

Paracetamol, unlike other common analgesics such as aspirin and ibuprofen, has no anti-inflammatory properties, and so it is not a member of the class of drugs known as non-steroidal anti-inflammatory drugs (NSAIDs). In recommended doses, paracetamol does not irritate the lining of the stomach, affect blood coagulation as much as NSAIDs, or affect function of the kidneys.

Paracetamol is safe in pregnancy, and does not affect the closure of the fetal ductus arteriosus (as NSAIDs can). Unlike aspirin, it is safe in children as paracetamol is not associated with a risk of Reye's syndrome in children with viral illnesses.

Like NSAIDs and unlike opioid analgesics, paracetamol has not been found to cause euphoria or alter mood in any way. Paracetamol and NSAIDs have the benefit of bearing a low risk of addiction, dependence, tolerance and withdrawal.

Paracetamol, particularly in combination with weak opioids, is more likely than NSAIDs to cause rebound headache (medication overuse headache), although less of a risk than ergotamine or triptans used for migraines.[5]

Toxicity

In humans, paracetamol has a narrow therapeutic index – the therapeutic dose is close to the toxic dose. Additionally, paracetamol is contained in many preparations (both over-the-counter and prescription only medications). In some other animals, for example cats, all doses are toxic. This means that, despite being one of the safest analgesics available at recommended doses, there is a large potential for overdose and toxicity.[6] Without timely treatment, paracetamol overdose can lead to liver failure and death within days. Because of the wide over-the-counter availability of the drug, it is sometimes used in suicide attempts by those unaware of the prolonged timecourse, and high morbidity (likelihood of significant illness) and mortality associated with paracetamol-induced toxicity.

In the UK, sales of over-the-counter Paracetamol in pharmacies are restricted to packs of 32 tablets per customer per occasion (only 16 tablets in non-pharmacy stores). In Ireland, the limits are 24 and 12 tablets respectively.

Mechanism of toxicity

As discussed above in the section regarding metabolism, paracetamol is mostly converted to inactive compounds via Phase II metabolism by conjugation with sulfate and glucuronide, with a small portion being oxidized via the cytochrome P450 enzyme system. Cytochrome P450 2E1 (CYP2E1) converts paracetamol to a highly reactive intermediary metabolite, N-acetyl-p-benzo-quinone imine (NAPQI).

Under normal conditions, NAPQI is detoxified by conjugation with glutathione. In cases of paracetamol toxicity, the sulfate and glucuronide pathways become saturated, and more paracetamol is shunted to the cytochrome P450 system to produce NAPQI. As a result, hepatocellular supplies of glutathione become exhausted and NAPQI is free to react with cellular membrane molecules, resulting in widespread hepatocyte damage and death, clinically leading to acute hepatic necrosis. In animal studies, 70% of hepatic glutathione must be depleted before hepatotoxicity occurs.

Toxic dose

The toxic dose of paracetamol is highly variable. In adults, single doses above 10 grams or 150 mg/kg have a reasonable likelihood of causing toxicity.[7] Toxicity can also occur when multiple smaller doses within 24 hours exceeds these levels, or even with chronic ingestion of doses as low as 4 g/day, and death with as little as 6 g/day.

In children acute doses above 200 mg/kg could potentially cause toxicity. This higher threshold is largely due to children having relatively larger kidneys and livers than adults and hence being more tolerant of paracetamol overdose than adults.[8] Acute paracetamol overdose in children rarely causes illness or death with chronic supratherapeutic doses being the major cause of toxicity in children.

Since paracetamol is often included in combination with other drugs, it is important to include all sources of paracetamol when checking a person's dose for toxicity. In addition to being sold by itself, paracetamol may be included in the formulations of various analgesics and cold/flu remedies as a way to increase the pain-relieving properties of the medication. To prevent overdoses, one should read medication labels carefully for the presence of paracetamol and check with a pharmacist before using over-the-counter medications.

Risk factors for toxicity

Chronic excessive ethanol (alcohol) consumption can induce CYP2E1, thus increasing the potential toxicity of paracetamol.[9] For this reason, other analgesics such as aspirin or ibuprofen are sometimes recommended for hangovers.

Fasting is a risk factor, possibly because of depletion of hepatic glutathione reserves.

It is well documented that concomitant use of the CYP2E1 inducer isoniazid increases the risk of hepatotoxicity, though whether CYP2E1 induction is related to the hepatotoxicity in this case is unclear.[10][11] Concomitant use of other drugs which induce CYP enzymes such as antiepileptics (including carbamazepine, phenytoin, barbituates, etc) have also been reported as risk factors.

Natural history

Individuals who have overdosed on paracetamol generally have no specific symptoms for the first 24 hours. Although nausea, vomiting, and diaphoresis may occur initially, these symptoms generally resolve after several hours. After resolution of these symptoms, individuals tend to feel better, and may believe that the worst is over. If a toxic dose was absorbed, after this brief feeling of relative wellness, the individual develops overt hepatic failure. In massive overdoses, coma and metabolic acidosis may occur prior to hepatic failure.

Damage generally occurs in hepatocytes as they metabolize the paracetamol. Rarely, acute renal failure also may occur. This is usually caused by either hepatorenal syndrome or Multiple organ dysfunction syndrome. Acute renal failure may also be the primary clinical manifestation of toxicity. In these cases, it has been suggested that the toxic metabolite is produced more in the kidneys than in the liver.[12]

The prognosis of paracetamol toxicity varies depending on the dose and the appropriate treatment. In some cases, massive hepatic necrosis leads to fulminant hepatic failure with complications of bleeding, hypoglycemia, renal failure, hepatic encephalopathy, cerebral edema, sepsis, multiple organ failure, and death within days. In many cases, the hepatic necrosis may run its course, hepatic function may return, and the patient may survive with liver function returning to normal in a few weeks.

Diagnosis

Evidence of liver toxicity may develop in 1 to 4 days, although in severe cases it may be evident in 12 hours. Right upper quadrant tenderness may be present. Laboratory studies may show evidence of massive hepatic necrosis with elevated AST, ALT, bilirubin, and prolonged coagulation times (particularly, elevated prothrombin time). After paracetamol overdose, when AST and ALT exceed 1000 IU/L, paracetamol-induced hepatotoxicity can be diagnosed. However, the AST and ALT levels can exceed 10,000 IU/L. Generally the AST is somewhat higher than the ALT in paracetamol-induced hepatotoxicity.

A drug nomogram was developed in 1975 which estimated the risk of toxicity based on the serum concentration of paracetamol at a given number of hours after ingestion.[13] To determine the risk of potential hepatotoxicity, the paracetamol level is traced along the standard nomogram. A paracetamol level drawn in the first four hours after ingestion may underestimate the amount in the system because paracetamol may still be in the process of being absorbed from the gastrointestinal tract. Delay of the initial draw for the paracetamol level to account for this is not recommended since the history in these cases is often poor and a toxic level at any time is a reason to give the antidote.

Treatment

Initial measures

The initial treatment for uncomplicated paracetamol overdose, similar to any other overdose, is gastrointestinal decontamination. In addition, the antidote, acetylcysteine plays an important role. Paracetamol absorption from the gastrointestinal tract is complete within 2 hours under normal circumstances, so decontamination is most helpful if performed within this timeframe. Absorption may be somewhat slowed when it is ingested with food. There is considerable room for physician judgement regarding gastrointestinal decontamination, activated carbon administration is the most commonly used procedure, however, gastric lavage may also be considered if the amount ingested is potentially life threatening and the procedure can be performed within 60 minutes of ingestion.[14] Syrup of ipecac has no role in paracetamol overdose because the vomiting it induces delays the effective administration of activated carbon and oral acetylcysteine.

Activated carbon adsorbs paracetamol, reducing its gastrointestinal absorption. Administering activated carbon also poses less risk of aspiration than gastric lavage. Previously there was reluctance to give activated carbon in paracetamol overdose, because of concern that it may also absorb acetylcysteine. Studies have shown that no more than 39% of an oral acetylcysteine is absorbed when they are administered together.[15] Other studies have shown that activated carbon seems to be beneficial to the clinical outcome. It appears the most benefit from activated carbon is gained if it is given with 2 hours of ingestion.[16] However, administering activated carbon later than this can be considered in patients who may have delayed gastric emptying due to co-ingested drugs or following ingestion of sustained or delayed release paracetamol preparations. Activated carbon should also be administered if co-ingested drugs warrant decontamination. There are conflicting recommendations[15][17] regarding whether to change the dosing of oral acetylcysteine after the administration of activated carbon, and even whether the dosing of acetylcysteine needs to be altered at all.

Acetylcysteine

Acetylcysteine works to reduce paracetamol toxicity by supplying sulfhydryl groups (mainly in the form of glutathione, of which it is a precursor) to react with the toxic NAPQI metabolite so that it does not damage cells and can be safely excreted.

If the patient presents less than 8 hours after paracetamol overdose, then acetylcysteine significantly reduces the risk of serious hepatotoxicity. If NAC is started more than 8 hours after ingestion, there is a sharp decline in its effectiveness because the cascade of toxic events in the liver has already begun and the risk of acute hepatic necrosis and death increases dramatically. Although acetylcysteine is most effective if given early, it still has beneficial effects if given as late as 48 hours after ingestion.[18] In clinical practice, if the patient presents more than 8 hours after the paracetamol overdose, then activated charcoal is probably not useful, and acetylcysteine is started immediately. In earlier presentations the

doctor can give charcoal as soon as the patient arrives, start giving acetylcysteine, and wait for the paracetamol level from the laboratory.

In United States practice, intravenous (IV) and oral administration are considered to be equally effective. However, IV is the only recommended route in Australasian and British practice.

Oral acetylcysteine is given as a 140 mg/kg loading dose followed by 70 mg/kg every 4 hours for 17 more doses. Oral acetylcysteine may be poorly tolerated due to its unpleasant taste, odor, and its tendency to cause nausea and vomiting. It can be diluted to a 5% solution, from its marketed 10% or 20% solutions, to improve palatability. Where oral acetylcysteine is required, the inhalation formulation of acetylcysteine (Mucomyst) is often given orally. The respiratory formulation can also be diluted and filter sterilized by a hospital pharmacist for IV use, however this is an uncommon practice. If repeat doses of charcoal are indicated because of another ingested drug, then subsequent doses of carbon and acetylcysteine should be staggered every two hours.

Intravenous acetylcysteine (Parvolex/Acetadote) is used as a continuous intravenous infusion over 20 hours (total dose 300 mg/kg). Recommended administration involves infusion of a 150 mg/kg loading dose over 15 minutes, followed by 50 mg/kg infusion over 4 hours; the last 100 mg/kg are infused over the remaining 16 hours of the protocol. Intravenous acetylcysteine has the advantage of shortening hospital stay, increasing both doctor and patient convenience, and it allows administration of activated carbon to reduce absorption of both the paracetamol and any co-ingested drugs without concerns about interference with oral acetylcysteine.[19]

Baseline laboratory studies include bilirubin, AST, ALT, and prothrombin time (with INR). Studies are repeated at least daily. Once it has been determined that a potentially toxic overdose has occurred, acetylcysteine is continued for the entire regimen, even after the paracetamol level becomes undetectable in the blood. If hepatic failure develops, acetylcysteine should be continued beyond the standard doses until hepatic function improves or until the patient has a liver transplant.

Prognosis

The mortality rate from paracetamol overdose increases 2 days after the ingestion, reaches a maximum on day 4, and then gradually decreases. Patients with a poor prognosis are usually identified for likely liver transplantation. Acidemia is the most important single indicator of probable mortality and the need for transplantation. A mortality rate of 95% without transplant was reported in patients who had a documented pH of < 7.30. Other indicators of poor prognosis include renal insufficiency, grade 3 or worse hepatic encephalopathy, a markedly elevated prothrombin time, or a rise in prothrombin time from day 3 to day 4. One study has shown that a factor V level less than 10% of normal indicated a poor prognosis (91% mortality) while a ratio of factor VIII to factor V of less than 30 indicated a good prognosis (100% survival).

Danger to animals

Paracetamol is extremely toxic to cats, and should not be given to them under any circumstances. Cats lack the necessary glucuronyl transferase enzymes to safely break paracetamol down and tiny fractions of a normal tablet for humans may prove fatal.[20]

In dogs paracetamol is a useful anti-inflammatory with a good safety record, causing a lower incidence of gastric ulceration than NSAIDs. It should only be administered on veterinary advice. A paracetamol codene product (Pardale-V)[2] licensed for use in dogs is available on veterinary prescription in the UK.

Any cases of suspected ingestion in cats or overdose in dogs should be taken to a veterinarian immediately for detoxification.[21] The effects of toxicity can include liver damage, haemolytic anaemia, oxidative damage to the red blood cells and bleeding tendencies. There are no home remedies, and the amount of irreversible liver failure is dependent on how quickly veterinary intervention begins. Treatment of paracetamol overdose by a veterinarian may involve the use of supportive fluid therapy, acetylcysteine (Mucomyst), methionine or s-adenosyl-l-methionine (SAMe) to slow liver damage and cimetidine (Tagamet) to protect against gastric ulceration. Once liver damage has occurred it cannot be reversed.[3]

November 2006 United States recall of generic paracetamol

On November 9, 2006, the U.S. Food and Drug Administration (FDA) announced a recall of approximately 11 million bottles of generic paracetamol manufactured by Perrigo, the largest manufacturer of generic over-the-counter drugs in the United States, due to metal particles having been found in a small sample of paracetamol caplets.[22] The recall is limited to 383 lots of 500 mg caplets; other lots and other dosages, as well as generic paracetamol from other manufacturers or proprietary formulations of paracetamol, are not affected. The complete list of recalled lots may be found on the FDA website.

As of November 14, 2006, no deaths or injuries have been reported as a result of the incident.

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Anaesthetics

A wide variety of drugs are used in modern anaesthetic practice. Many are rarely used outside of anaesthesia, although others are used commonly by all disciplines. Some of the prominent ones include:

- local anaesthetics
  - general anaesthetics
    - inhalational anaesthetics
      - volatile anaesthetics
        - desflurane

sevoflurane
isoflurane
halothane
enflurane
methoxyflurane

- nitrous oxide
  - xenon
- intravenous anaesthetics
  - propofol

etomidate

- barbiturates
  - methohexital

thiopentone/thiopental

- benzodiazepines
  - midazolam
  - diazepam
- ketamine

- analgesics
  - opioids
    - morphine
    - fentanyl

- alfentanil
sufentanil
remifentanil

- methadone

- meperidine / pethidine
- NSAIDs

- muscle relaxants
  - depolarising muscle relaxants
    - succinylcholine, also known as suxamethonium
  - nondepolarising (curare-like) muscle relaxants
    - atracurium
cisatracurium
vecuronium
rocuronium
mivacurium
tubocurarine (see mislabelled article "turbocurnanine" under "search." Can this article be placed correctly under tubocurarine also?)
pancuronium bromide
- vasoconstrictors, also known as vasopressors
  - phenylephrine
  - Ephedrine
  - metaraminol
- antiemetics: phenothiazines, e.g.: prochlorperazine, promethazine, cyclizine;

butyrophenones, e.g.: droperidol; antihistamines, e.g.: dimenhydrinate (old); newer agents: ondansetron and tropisetron, and granisetron; steroids, e.g.: dexamethasone; and lastly, metoclopramide (variable efficacy).

Local anesthetics

A *local anesthetic* is a drug that reversibly inhibits the propagation of signals along nerves. When it is used on specific nerve pathways, effects such as analgesia (loss of pain sensation) and paralysis (loss of muscle power) can be achieved.

Clinical local anesthetics belong to one of two classes: aminoamide and aminoester local anesthetics. These so-called synthetic local anesthetics are structurally related to cocaine. They differ from cocaine mainly in that they have no abuse potential and do not act on the sympathoadrenergic system, i.e. they do not produce hypertension or local vasoconstriction.

Local anesthetics vary in their pharmacological properties and they are used in various techniques of local anesthesia such as:

- Topical anesthesia (surface)
- Infiltration
- Plexus block
- Epidural (extradural) block
- Spinal anesthesia

The local anesthetic lidocaine is also used as a Class Ib antiarrhythmic drug.

Mechanism of action

Local anesthetic drugs act mainly by inhibiting sodium influx through sodium-specific ion channels in the neuronal cell membrane, in particular the so-called voltage-gated sodium channels. When the influx of sodium is interrupted, an action potential cannot arise and signal conduction is inhibited. The receptor site is thought to be located at the cytoplasmic (inner) portion of the sodium channel. Local anesthetic drugs bind more readily to "open" sodium channels, thus onset of neuronal blockade is faster in neurons that are rapidly firing. This is referred to as state dependent blockade.

Local anesthetics are weak bases and are usually formulated as the hydrochloride salt to render them water-soluble. At physiologic pH the protonated (ionised) and unprotonated (unionised) forms of the molecule exist in an equilibrium but only the unprotonated molecule diffuses readily across cell membranes. Once inside the cell, the lower pH results in the molecule being protonated, thus inhibiting its passage back out of the cell. This is referred to as "ion-trapping". In the protonated form, the molecule binds to the local anaesthetic binding site on the inside of the ion channel near the cytoplasmic end.

Acidosis such as caused by wound infection partly reduces the action of local anesthetics. This is partly because most of the anaesthetic is ionised and therefore unable to cross the cell membrane.

Undesired effects

The conduction of electric impulses follows a similar mechanism in peripheral nerves, the central nervous system, and the heart. The effects of local anesthetics are therefore not specific for the signal conduction in peripheral nerves. Side effects on the central nervous system and the heart may be severe and potentially fatal. However, toxicity usually occurs only at blood plasma levels which are rarely reached if proper anesthetic techniques are adhered to.

Central nervous system

Depending on local tissue concentrations of local anesthetics, there may be excitatory or depressant effects on the central nervous system. At lower concentrations, a relatively selective depression of inhibitory neurons results in cerebral excitation, which may lead to generalized convulsions. A profound depression of brain functions occurs at higher concentrations which may lead to coma, respiratory arrest and death. Such tissue concentrations may be due to very high plasma levels after intravenous injection of a large

dose. Another possibility is direct exposure of the central nervous system through the cerebrospinal fluid, i.e. overdose in spinal anesthesia or accidental injection into the subarachnoid space in epidural anesthesia.

Cardiovascular system

The conductive system of the heart is quite sensitive to the action of local anesthetics. Lidocaine is often used as an antiarrhythmic drug and has been studied extensively, but the effects of other local anesthetics are probably similar to those of Lidocaine. Lidocaine acts by blocking sodium channels, leading to slowed conduction of impulses. This may obviously result in bradycardia, but tachyarrhythmia can also occur. With high plasma levels of lidocaine there may be higher-degree atrioventricular block and severe bradycardia, leading to coma and possibly death.

Treatment of overdose

There is evidence that Intralipid, a commonly available intravenous lipid emulsion, can be effective in treating severe cardiotoxicity secondary to local anaesthetic overdose, including human case reports of successful use in this way ('lipid rescue').[1][2][3]

Hypersensitivity/Allergy

Adverse reactions to local anesthetics are not infrequent, but true allergy is very rare. Non-allergic reactions may resemble allergy in their manifestations. In some cases, skin tests and provocative challenge may be necessary to establish a diagnosis of allergy. There are also cases of allergy to paraben derivatives, which are often added as preservatives to local anesthetic solutions.

Methemoglobinemia

The systemic toxicity of prilocaine is comparatively low, however its metabolite, o-toluidine, is known to cause methemoglobinemia. As methemoglobinemia reduces the amount of hemoglobin that is available for oxygen transport, this side effect is potentially life-threatening. Therefore dose limits for prilocaine should be strictly observed. Prilocaine is not recommended for use in infants.

Local anesthetics in clinical use

- Amino esters
  - Benzocaine
  - Chloroprocaine
  - Cocaine
  - Procaine
- Amino amides
  - Bupivacaine
  - Levobupivacaine
  - Lidocaine
  - Mepivacaine
  - Prilocaine
  - Ropivacaine
- Combinations
  - Lidocaine/prilocaine (EMLA)

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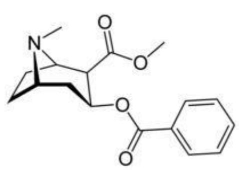
See also

- Anesthetic

Cocaine



Systematic (IUPAC) name

methyl (1R,2R,3S,5S)-3-(benzoyloxy)-8-methyl-8-azabicyclo[3.2.1]octane-2-carboxylate

Identifiers

CAS number 50-36-2

ATC code N01**BC01** R02**AD03**, S01**HA01**, S02**DA02**

PubChem 5760

DrugBank APRD00080

Chemical data

Formula $C_{17}H_{21}NO_4$

Mol. weight 303.353 g/mol

Physical data

Melt. point 195 °C (383 °F)

Solubility in water 1800 mg/mL (20 °C)

Pharmacokinetic data

Bioavailability Oral: 30%, Nasal: 30-60% [1]

Metabolism Hepatic CYP3A4

Half life 1 hour

Excretion Renal (benzoylecgonine and ecgonine methyl ester)

Therapeutic considerations

Pregnancy cat. C

Legal status Schedule I(CA) Class A(UK) Schedule II(US)

Dependence Liability Medium

Routes Topical, Oral, Insufflation, IV, PO

Cocaine is a crystalline tropane alkaloid that is obtained from the leaves of the coca plant. It is a stimulant of the central nervous system and an appetite suppressant, creating what has been described as a euphoric sense of happiness and increased energy. Though most often used recreationally for this effect, cocaine is also a topical anesthetic used in eye, throat, and nose surgery. Cocaine can be psychologically addictive, and its possession, cultivation, and distribution is illegal for non-medicinal and non-government sanctioned purposes in virtually all parts of the world. The name comes from the name of the coca plant plus the alkaloid suffix -ine.

The stimulating qualities of the coca leaf were known to the ancient peoples of Peru and other Pre-Columbian South American societies. In modern Western countries, cocaine has been a feature of the counterculture for well-over a century; there is a long-list of prominent intellectuals, artists, and musicians who have used the drug — names ranging from Sir Arthur Conan Doyle and Sigmund Freud to United States President Ulysses S. Grant. For several decades after its initial release, cocaine could be found in trace amounts in the Coca-Cola beverage. Today, although illegal in virtually all countries, cocaine remains popular in a wide variety of social and personal settings.

History

The coca leaf

South American indigenous peoples have chewed the coca leaf (Erythroxylum coca), a plant that contains vital nutrients as well as numerous alkaloids, including cocaine. The leaf

was, and is, chewed almost universally by some indigenous communities—ancient Peruvian mummies have been found with the remains of coca leaves deposited in their mouths, and pottery from the time period depicts humans whose cheeks are bulged with the presence of something on which they are chewing.[2]However, it should be noted that there is no evidence that its habitual use has ever led to any of the negative consequences generally associated with habitual cocaine use today.[3][4] There is evidence that these cultures used a mixture of coca leaves and saliva as an anesthetic for the performance of trepanation.[5]

When the Spaniards colonized South America, they at first ignored aboriginal claims that the leaf gave them strength and energy, and declared the chewing of coca leaves a satanic practice. But after discovering that these claims were true, they legalized and taxed the leaf, taking 10 percent off the value of each crop. These taxes were for a time the main source of support for the Roman Catholic Church in the region. In 1569, Nicholas Monardes described the practice of the natives of chewing a mixture of tobacco and coca leaves to induce "great contentment":

"[...when they wished to] make themselves drunk and [...] out of judgment [they chewed a mixture of tobacco and coca leaves which...] make them go as they were out of their wittes [...]"

[6]

In 1609, Padre Blas Valera wrote:

"Coca protects the body from many ailments, and our doctors use it in powdered form to reduce the swelling of wounds, to strengthen broken bones, to expel cold from the body or prevent it from entering, and to cure rotten wounds or sores that are full of maggots. And if it does so much for outward ailments, will not its singular virtue have even greater effect in the entrails of those who eat it?"

Isolation

Although the stimulant and hunger-suppressant properties of coca had been known for many centuries, the isolation of the cocaine alkaloid was not achieved until 1855. Many scientists had attempted to isolate cocaine, but none had been successful for two reasons: the knowledge of chemistry required was insufficient at the time, worsened because coca does not grow in Europe and ruins easily during travel.

The cocaine alkaloid was first isolated by the German chemist Friedrich Gaedcke in 1855. Gaedcke named the alkaloid “erythroxyline,” and published a description in the journal Archives de Pharmacie.

In 1856, Friedrich Wöhler asked Dr. Carl Scherzer, a scientist aboard the Novara (an Austrian frigate sent by Emperor Franz Joseph to circle the globe), to bring him a large amount of coca leaves from South America. In 1859, the ship finished its travels and Wöhler received a trunk full of coca. Wöhler passed on the leaves to Albert Niemann, a Ph.D. student at the University of Göttingen in Germany, who then developed an improved purification process.

Niemann described every step he took to isolate cocaine in his dissertation titled Über eine neue organische Base in den Cocablättern (On a New Organic Base in the Coca Leaves), which was published in 1860—it earned him his Ph. D. and is now in the British Library. He wrote of the alkaloid's “colourless transparent prisms” and said that, “Its solutions have an alkaline reaction, a bitter taste, promote the flow of saliva and leave a peculiar numbness, followed by a sense of cold when applied to the tongue.” Niemann named the alkaloid “Cocain”—as with other alkaloids its name carried the “-in” ending (derived from the Latin suffix -ina).

Medicalization

With the discovery of this new alkaloid, Western medicine was quick to jump upon and exploit the possible uses of this plant.

In 1879, Vassili von Anrep, of the University of Würzburg, devised an experiment to demonstrate the analgesic properties of the newly-discovered alkaloid. He prepared two separate jars, one containing a cocaine-salt solution, with the other containing merely salt water. He then submerged a frog's legs into the two jars, one leg in the treatment and one in the control solution, and proceeded to stimulate the legs in several different ways. The leg that had been immersed in the cocaine solution reacted very differently than the leg that had been immersed in salt water.[7]

Carl Koller (a close associate of Sigmund Freud, who would write about cocaine later) experimented with cocaine for ophthalmic usage. In an infamous experiment in 1884, he experimented upon himself by applying a cocaine solution to his own eye and then pricking it with pins. His findings were presented to the Heidelberg Ophthalmological Society. Also in 1884, Jellinek demonstrated the effects of cocaine as a respiratory system anesthetic. In 1885, William Halsted demonstrated nerve-block anesthesia,[8] and James Corning demonstrated peridural anesthesia.[9] 1898 saw Heinrich Quincke use cocaine for spinal anesthesia.

Popularization

In 1859, an Italian doctor, Paolo Mantegazza returned from Peru, where he had witnessed first-hand the use of coca by the natives. He proceeded to experiment on himself and upon his return to Milan he wrote a paper in which he described the effects. In this paper he declared coca and cocaine (at the time they were assumed to be the same) as being useful medicinally, in the treatment of “a furred tongue in the morning, flatulence, [and] whitening of the teeth.”

A chemist named Angelo Mariani who read Mantegazza’s paper became immediately intrigued with coca and its economic potential. In 1863, Mariani started marketing a wine called Vin Mariani, which had been treated with coca leaves. The ethanol in wine acted as a solvent and extracted the cocaine from the coca leaves, altering the drink’s effect. It contained 6 mg cocaine per ounce of wine, but Vin Mariani, which was to be exported, contained 7.2 mg per ounce to compete with the higher cocaine content of similar drinks in the United States. A “pinch of coca leaves” was included in John Styth Pemberton's original

1886 recipe for Coca-Cola, though the company began using decocainized leaves in 1906 when the Pure Food and Drug Act was passed. The only known measure of the amount of cocaine in Coca-Cola was determined in 1902 as being as little as 1/400 of a grain (0.2 mg) per ounce of syrup (6 ppm). The actual amount of cocaine that Coca-Cola contained during the first twenty years of its production is practically impossible to determine.

In 1879 cocaine began to be used to treat morphine addiction. Cocaine was introduced into clinical use as a local anaesthetic in Germany in 1884, about the same time as Sigmund Freud published his work Über Coca (On Coca), in which he wrote that cocaine causes:

"...exhilaration and lasting euphoria, which in no way differs from the normal euphoria of the healthy person...You perceive an increase of self-control and possess more vitality and capacity for work....In other words, you are simply normal, and it is soon hard to believe you are under the influence of any drug....Long intensive physical work is performed without any fatigue...This result is enjoyed without any of the unpleasant after-effects that follow exhilaration brought about by alcohol....Absolutely no craving for the further use of cocaine appears after the first, or even after repeated taking of the drug..."

In 1885 the U.S. manufacturer Parke-Davis sold cocaine in various forms, including cigarettes, powder, and even a cocaine mixture that could be injected directly into the user's veins with the included needle. The company promised that its cocaine products would "supply the place of food, make the coward brave, the silent eloquent and... render the sufferer insensitive to pain."

By the late Victorian era cocaine use had appeared as a vice in literature; for example, Arthur Conan Doyle's fictional Sherlock Holmes injects a "seven-percent solution" of the drug in The Sign of Four.

In 1909, Ernest Shackleton took "Forced March" brand cocaine tablets to Antarctica, as did Captain Scott a year later on his ill-fated journey to the South Pole.[10] Even as late as 1938, the Larousse Gastronomique was published carrying a recipe for "cocaine pudding".

Prohibition

By the turn of the twentieth century, the addictive properties of cocaine had become clear to many, and the problem of cocaine abuse began to capture public attention in the United States. The dangers of cocaine abuse became part of a moral panic that was tied to the dominant racial and social anxieties of the day. In 1903, the American Journal of Pharmacy stressed that most cocaine abusers were "bohemians, gamblers, high- and low-class prostitutes, night porters, bell boys, burglars, racketeers, pimps, and casual laborers." In 1914, Dr. Christopher Koch of Pennsylvania's State Pharmacy Board made the racial innuendo explicit, testifying that, "Most of the attacks upon the white women of the South are the direct result of a cocaine-crazed Negro brain."[citation needed] Mass media created an epidemic of cocaine use among African Americans in the Southern United States to play upon racial prejudices of the era, though there is little evidence that such an epidemic actually took place. In the same year, the Harrison Narcotics Tax Act outlawed the use of cocaine in the United States. This law incorrectly referred to cocaine as a narcotic, and the

misclassification passed into popular culture. As stated above, cocaine is a stimulant, not a narcotic.

Modern usage

In many countries, cocaine is a popular recreational drug. In the United States, the development of "crack" cocaine introduced the substance to a generally poorer inner-city market. Use of the powder form has stayed relatively constant, experiencing a new height of use during the late 1990's, however, use has dropped somewhat from the early 2000's giving way to MDMA which has increased in popularity. Cocaine has become much more popular in the last few years in the UK.

Cocaine use is prevalent across all socioeconomic strata, including age, demographics, economic, social, political, religious, and livelihood. Cocaine in its various forms comes in second only to cannabis as the most popular illegal recreational drug in the United States, and is number one in street value sold each year.

The estimated U.S. cocaine market exceeded $35 billion in street value for the year 2003. There is a tremendous demand for cocaine in the U.S. market, particularly among those who are making incomes affording luxury spending, such as single adults and various professionals. Cocaine's status as a club drug shows its immense popularity among the "party crowd."

In 1995 the World Health Organization (WHO) and the United Nations Interregional Crime and Justice Research Institute (UNICRI) announced in a press release the publication of the results of the largest global study on cocaine use ever undertaken. However, a decision in the World Health Assembly banned the publication of the study. In the sixth meeting of the B committee the US representative threatened that "If WHO activities relating to drugs failed to reinforce proven drug control approaches, funds for the relevant programmes should be curtailed". This led to the decision to discontinue publication. A part of the study has been recuperated.[11] Available are profiles of cocaine use in 20 countries. Some of the findings were that "Generally cocaine users consume a range of other drugs as well. There appears to be very little 'pure' cocaine use. Overall, fewer people in participating countries have used cocaine than have used alcohol, tobacco or cannabis. Also, in most countries, cocaine is not the drug associated with the greatest problems.", "There is a complex relationship between cocaine use and crime, particularly theft and violence.", "In most participating countries, a minority of people start using cocaine or related products, use casually for a short or long period, and suffer little or no negative consequences, even after years of use. This suggests it is possible to reduce, if not entirely eliminate, harmful cocaine use."[12]

A problem with illegal cocaine use, especially in the higher volumes used to combat fatigue (rather than increase euphoria) by long-term users is trauma caused by the compounds used in adulteration. Cutting or "stamping on" the drug is commonplace, using compounds which simulate ingestion effects, such as novocaine producing temporary anasthaesia, ephedrine producing an increased heart rate, or more dangerously, strong toxins to produce vasodilatory effects. For example a nosebleed is foolishly regarded by heavy users as a sign of purity. The normal adulterants for profit are inactive sugars, usually mannitol, creatine or glucose, so introducing active adulterants gives the illusion of purity. Cocaine trading carries large penalties in most jurisdictions, so user deception about purity and consequent high profits for dealers are the norm.

Pharmacology

Appearance

Cocaine in its purest form is a white, pearly product. Cocaine appearing in powder form is a salt, typically cocaine hydrochloride (CAS 53-21-4). Black market cocaine is frequently adulterated or "cut" with various powdery fillers to increase its surface area; the substances most commonly used in this process are baking soda; sugars, such as lactose, dextrose, inositol, and mannitol; and local anesthetics, such as lidocaine or benzocaine, which mimic or add to cocaine's numbing effect on mucous membranes. Cocaine may also be "cut" with other stimulants such as methamphetamine. Adulterated cocaine is often a white, off-white or pinkish powder. Novacaine, a dental anesthetic and benzocaine (an ingredient used in Anbesol and other non-prescription oral anesthetics) are related to cocaine and can both cause a person to test positive for it even though they are not using illegal drugs.

The color of "crack" cocaine depends upon several factors including the origin of the cocaine used, the method of preparation – with ammonia or sodium bicarbonate – and the presence of impurities, but will generally range from white to a yellowish creme to a light brown. Its texture will also depend on the adulterants, origin and processing of the powdered cocaine, and the method of converting the base; but will range from a crumbly texture, sometimes extremely oily, to a hard, almost crystalline nature.

Forms of cocaine

Cocaine sulfate

Cocaine sulfate is produced by macerating coca leaves along with water that has been acidulated with sulfuric acid, or a aromatic-based solvent, like kerosene or benzene. This is often accomplished by putting the ingredients into a vat and stamping on it, in a manner similar to the traditional method for crushing grapes. After the cocaine is extracted, the water is evaporated to yield a pasty mass of impure cocaine sulfate.

The sulfate itself is an intermediate step to producing cocaine hydrochloride. In South America, it is commonly smoked along with tobacco, and is known as pasta, basuco, basa, pitillo, paco or simply paste. It is also gaining popularity as a cheap drug (.30-.70 U.S. cents per "hit" or dose) in Argentina.

Freebase

As the name implies, "freebase" is the base form of cocaine, as opposed to the salt form of cocaine hydrochloride. Whereas cocaine hydrochloride is extremely soluble in water, cocaine base is insoluble in water and is therefore not suitable for drinking, snorting or injecting. Cocaine hydrochloride is not well-suited for smoking because the temperature at

which it vaporizes is very high, and close to the temperature at which it burns; however, cocaine base vaporizes at a low temperature, which makes it suitable for inhalation.

Smoking freebase is preferred by many users because the cocaine is absorbed immediately into blood via the lungs, where it reaches the brain in about five seconds. The rush is much more intense than sniffing the same amount of cocaine nasally, but the effects do not last as long. The peak of the freebase rush is over almost as soon as the user exhales the vapor, but the high typically lasts 5–10 minutes afterward. What makes freebasing particularly dangerous is that users typically don't wait that long for their next hit and will continue to smoke freebase until none is left. These effects are similar to those that can be achieved by injecting or “slamming” cocaine hydrochloride, but without the risks associated with intravenous drug use (though there are other serious risks associated with smoking freebase).

Freebase cocaine is produced by first dissolving cocaine hydrochloride in water. Once dissolved in water, cocaine hydrochloride (Coc HCl) dissociates into protonated cocaine ion (Coc-H+) and chloride ion (Cl–). Any solids that remain in the solution are not cocaine (they are part of the cut) and are removed by filtering. A base, typically ammonia (NH3), is added to the solution. The following net chemical reaction takes place:

$$\text{Coc-H}^{+}\text{Cl}^{-} + \text{NH}_3 \rightarrow \text{Coc} + \text{NH}_4\text{Cl}$$

As freebase cocaine (Coc) is insoluble in water, it precipitates and the solution becomes cloudy. To recover the freebase, a nonpolar solvent like diethyl ether is added to the solution: Because freebase is highly soluble in ether, a vigorous shaking of the mixture results in the freebase being dissolved in the ether. As ether is insoluble in water, it can be siphoned off. The ether is then evaporated, leaving behind the cocaine base.

Handling diethyl ether is dangerous because ether is extremely flammable, its vapors are heavier than air and can “creep” from an open bottle, and in the presence of oxygen it can form peroxides, which can spontaneously combust. Demonstrative of the dangers of the practice, the famous comedian Richard Pryor used to perform a well known skit in which he poked fun at himself over a 1980 incident in which he caused an explosion and set himself on fire while attempting to smoke “freebase”, presumably while still wet with ether.

Crack cocaine

Due to the dangers of using ether to produce pure freebase cocaine, cocaine producers began to omit the step of removing the freebase cocaine precipitate from the ammonia mixture. Typically, filtration processes are also omitted. The end result of this process is that the cut, in addition to the ammonium salt (NH_4Cl), remains in the freebase cocaine after the mixture is evaporated. The “rock” that is thus formed also contains a small amount of water. Sodium bicarbonate is also preferred in preparing the freebase, for when commonly "cooked" the ratio is 50/50 to 40/60 percent cocaine/bicarbonate. This acts as a filler which extends the overall profitability of illicit sales. Crack cocaine may be reprocessed in small quantities with water (users refer to the resultant product as "cookback"). This removes the

residual bicarbonate, and any adulterants or cuts that have been used in the previous handling of the cocaine and leaves a relatively pure, anhydrous cocaine base.

When the rock is heated, this water boils, making a crackling sound (hence the onomatopoeic “crack”). Baking soda is now most often used as a base rather than ammonia for reasons of lowered stench and toxicity; however, any weak base can be used to make crack cocaine. Strong bases, such as sodium hydroxide, tend to hydrolyze some of the cocaine into non-psychoactive ecgonine.

The net reaction when using baking soda (also called sodium bicarbonate, with a chemical formula of $NaHCO_3$) is:

$$Coc\text{-}H^+Cl^- + NaHCO_3 \rightarrow Coc + H_2O + CO_2 + NaCl$$

Crack is unique because it offers a strong cocaine experience in small, low-priced packages. In the United States, crack cocaine is often sold in small, inexpensive dosage units frequently known as “nickels”, “nickel rocks”, or "bumps" (referring to the price of $5.00), and also “dimes”, “dime rocks”, or "boulders" and sometimes as “twenties”, “solids", "slabs" and “forties.” The quantity provided by such a purchase varies depending upon many factors, such as local availability, which is affected by geographic location. A twenty may yield a quarter gram or half gram on average, yielding 30 minutes to an hour of effect if hits are taken every few minutes. After the $20 or $40 mark, crack and powder cocaine are sold in grams or fractions of ounces. At the intermediate level, crack cocaine is sold either by weight in ounces, referred to by terms such as "eight-ball" (one-eighth of an ounce) or "quarter" and "half" respectively. In the alternate, $20 pieces of crack cocaine are aggregated in units of "fifty pack" and "hundred pack", referring to the number of pieces. At this level, the wholesale price is approximately half the street sale price.

Crack cocaine was extremely popular in the mid- and late 1980s in a period known as the Crack Epidemic, especially in inner cities, though its popularity declined through the 1990s in the United States. There were major anti-drug campaigns launched in the U.S. to try and cull its popularity, the most popular being a series of ads featuring the slogan "The Thrill Can Kill".[13] However, there has been an increase in popularity within Canada in the recent years, where it has been estimated that the drug has become a multi-billion dollar 'industry'. Due to its popularity, there are many different street names for crack cocaine.

Although consisting of the same active drug as powder cocaine, crack cocaine in the United States is seen as a drug primarily by and for the inner-city poor; the stereotypical "crack head" is a poor, urban, usually homeless. While insufflated powder cocaine has an associated glamour attributed to its popularity among mostly middle and upper class whites (as well as musicians and entertainers), crack is perceived as a skid row drug of squalor and desperation. The U.S. federal trafficking penalties deal far more harshly towards crack when compared to powdered cocaine. Possession of five grams of crack (or over 500 grams of powder) carries a minimum sentence of five years imprisonment in the US.[14]

Modes of administration

Chewed/eaten

Coca leaves typically are mixed with an alkaline substance (such as lime) and chewed into a wad that is retained in the mouth between gum and cheek and sucked of its juices. The juices are absorbed slowly by the mucous membrane of the inner cheek and by the gastro-intestinal tract when swallowed. Alternatively, coca leaves can be infused in liquid and consumed like tea. Ingesting coca leaves generally is an inefficient means of administering cocaine. It should be remembered that the coca leaf is not actual cocaine, and is not a drug of any kind. Because cocaine is hydrolyzed (rendered inactive) in the acidic stomach, it is not readily absorbed. Only when mixed with a highly alkaline substance (such as lime) can it be absorbed into the bloodstream through the stomach. Absorption of orally administered cocaine is limited by two additional factors. First, the drug is partly metabolized in the liver. Second, capillaries in the mouth and esophagus constrict after contact with the drug, reducing the surface area over which the drug can be absorbed.

Orally administered cocaine takes approximately 30 minutes to enter the bloodstream. Typically, only 30 percent of an oral dose is absorbed, although absorption has been shown to reach 60 percent in controlled settings. Given the slow rate of absorption, maximum physiological and psychotropic effects are attained approximately 60 minutes after cocaine is administered by ingestion. While the onset of these effects is slow, the effects are sustained for approximately 60 minutes after their peak is attained.

Contrary to popular belief, both ingestion and insufflation result in approximately the same proportion of the drug being absorbed: 30 to 60 percent. G. Barnett, R. Hawks and R. Resnick, "Cocaine Pharmacokinetics in Humans," 3 Journal of Ethnopharmacology 353 (1981); Jones, supra note 19; Wilkinson et al., Van Dyke et al., Compared to ingestion, the faster absorption of insufflated cocaine results in quicker attainment of maximum drug effects. Snorting cocaine produces maximum physiological effects within 40 minutes and maximum psychotropic effects within 20 minutes, However a more realistic activation period is closer to 5 to 10 minutes, which is similar to ingestion of cocaine. Physiological and psychotropic effects from nasally insufflated cocaine are sustained for approximately 40 - 60 minutes after the peak effects are attained. Van Dyke, et al.

Mate de coca or coca-leaf tea is also a traditional method of consumption and is often recommended to treat altitude sickness. This method of consumption has been practiced for thousands of years by South American natives. One specific purpose of ancient coca leaf consumption was to increase energy and reduce fatigue in messengers who made multi-day quests to other settlements.

In 1986 an article in the Journal of the American Medical Association revealed that health food stores were selling coca-leaf tea as “Health Inca Tea.”[15] While the packaging claimed it had been “decocainized,” no such process had taken place—they were selling a controlled substance off the shelves. The article stated that drinking two cups of the tea per day gave a mild stimulation, increased heart rate, and mood elevation, and the tea was essentially harmless. Despite this, the DEA seized several shipments in Hawaii, Chicago, Illinois, Georgia,

and several locations on the East Coast of the United States, and the product was removed from the shelves.[10]

Insufflation

Insufflation (known colloquially as “snorting," “sniffing," or "blowing") is the most common method of ingestion of recreational powder cocaine in the Western world. Contrary to widespread belief, cocaine is not actually inhaled using this method; rather the drug coats and is absorbed through the mucous membranes lining the sinuses. When insufflating cocaine, absorption through the nasal membranes is approximately 30-60 percent, with higher doses leading to increased absorption efficiency. Any material not directly absorbed through the mucous membranes is collected in mucus and swallowed (this "drip" is considered pleasant by some and unpleasant by others). In a study[16] of cocaine users, the average time taken to reach peak subjective effects was 14.6 minutes. Chronic use results in ongoing rhinitis and necrosis of the nasal membranes. Many users report a burning sensation in the nares (nostrils) after cocaine's anasthetic effects wear off. Any damage to the inside of the nose is because cocaine highly constricts blood vessels — and therefore blood & oxygen/nutrient flow-- to that area. If this restriction of adequate blood supply is bad enough and, especially prolonged enough, the tissue there can die.

Prior to insufflation, cocaine powder must be divided into very fine particles. Cocaine of high purity breaks into fine dust very easily, except when it is moist (not well stored) and forms “chunks,” which reduces the efficiency of nasal absorption.

Rolled up banknotes, hollowed-out pens, cut straws, pointed ends of keys, and specialized spoons are often used to insufflate cocaine. Such devices are often referred to as "tooters" by users. The cocaine typically is poured onto a flat, hard surface (such as a mirror) and divided into "lines", which are then insufflated. The amount of cocaine in a line varies widely from person to person and occasion to occasion (the purity of the cocaine is also a factor), but one line is generally considered to be a single dose and is typically 35mg-100mg. However as tolerance builds rapidly in the short-term (hours), many lines are often snorted to produce greater effects.

Injected

Drug injection provides the highest blood levels of drug in the shortest amount of time. Upon injection, cocaine reaches the brain in a matter of seconds, and the exhilarating rush that follows can be so intense that it induces some users to vomit uncontrollably. In a study[16] of cocaine users, the average time taken to reach peak subjective effects was 3.1 minutes. The euphoria passes quickly. Aside from the toxic effects of cocaine, there is also danger of circulatory emboli from the insoluble substances that may be used to cut the drug. There is also a risk of serious infection associated with the use of contaminated needles.

An injected mixture of cocaine and heroin, known as “speedball” or “moonrock”, is a particularly popular and dangerous combination, as the converse effects of the drugs actually complement each other, but may also mask the symptoms of an overdose. It has

been responsible for numerous deaths, particularly in and around Los Angeles, including celebrities such as John Belushi, Chris Farley, Layne Staley and River Phoenix. Experimentally, cocaine injections can be delivered to animals such as fruit flies to study the mechanisms of cocaine addiction.[17]

Smoked

Smoking freebase or crack cocaine is most often accomplished using a pipe made from a small glass tube about one quarter-inch (about 6 mm) in diameter and on the average, four inches long. These are sometimes called "stems", "horns", "blasters" and "straight shooters," readily available in convenience stores or smoke shops. They will sometimes contain a small paper flower and are promoted as a romantic gift. Buyers usually ask for a "rose" or a "flower." An alternate method is to use a small length of a radio antenna or similar metal tube. To avoid burning the user's fingers and lips on the metal pipe, a small piece of paper or cardboard (such as a piece torn from a matchbook cover) is wrapped around one end of the pipe and held in place with either a rubber band or a piece of adhesive tape. A popular (usually pejorative) term for crack pipes is "glass dick."

A small piece (approximately one inch) of heavy steel or copper scouring pad — often called a "brillo" or "chore", from the scouring pads of the same name — is placed into one end of the tube and carefully packed down to approximately three-quarter inch. Prior to insertion, the "brillo" is burnt off, to remove any oily coatings that may be present. It then serves as a reduction base and flow modulator in which the "rock" can melt and boil to vapor.

Another option is to use a deep socket, say 12mm, wrapped with electrical tape. Instead of Chore Boy, users typically employ high grade (very fine) speaker wire rolled into a ball as the filter medium. A Zippo lighter is recommended because of the stronger flame, but the taste of butane is quite noticeable. However, the socket is practically indestructible and inconspicuous.

The "rock" is placed at the end of the pipe closest to the filter and the other end of the pipe is placed in the mouth. A flame from a cigarette lighter or handheld torch is then held under the rock. As the rock is heated, it melts and burns away to vapor, which the user inhales as smoke. The effects, felt almost immediately after smoking, are very intense and do not last long — usually five to fifteen minutes. In a study[16] of cocaine users, the average time taken to reach peak subjective effects was 1.4 minutes. Most users will want more after this time, especially frequent users. "Crack houses" depend on these cravings by providing users a place to smoke, and a ready supply of small bags for sale.

A heavily used crackpipe tends to fracture at the end from overheating with the flame used to heat the crack as the user attempts to inhale every bit of the drug on the metal wool filter. The end is often broken further as the user "pushes" the pipe. "Pushing" is a technique used to partially recover crack that hardens on the inside wall of the pipe as the pipe cools. The user pushes the metal wool filter through the pipe from one end to the other to collect the build-up inside the pipe, which is a very pure and potent form of the base. The ends of the pipe can be broken by the object used to push the filter, frequently a small screwdriver or stiff piece of wire. The user will often remove the most jagged edges and continue using the pipe until it becomes so short that it burns the lips and fingers. To continue using the

pipe, the user will sometimes wrap a small piece of paper or cardboard around one end and hold it in place with a rubber band or adhesive tape. Of course, not all people who smoke crack cocaine will let it get that short, and will get a new or different pipe. The tell-tale signs of a used crack pipe are a glass tube with burn marks at one or both ends and a clump of metal wool inside. The language used to refer to the paraphernalia and practices of smoking cocaine vary tremendously across regions of the United States, as do the packaging methods utilized in the street level sale.

When smoked, cocaine is sometimes combined with other drugs, such as cannabis; often rolled into a joint or blunt. This combination is known as "primo", "hype", "shake and bake",a "turbo" a "yolabowla" "SnowCaps", "B-151er", a "cocoapuff", a "dirty" a "woo", or "geeking." Crack smokers who are being drug tested may also make their "primo" with cigarette tobacco instead of cannabis, since a crack smoker can test clean within two to three days of use, if only urine (and not hair) is being tested.

Powder cocaine is sometimes smoked, but it is inefficient as the heat involved destroys much of the chemical. One way of smoking powder is to put a "bump" into the end of an unlit cigarette, smoking it in one go as the user lights the cigarette normally.

Oral

Cocaine can aid as an oral anesthetic. Many users rub the powder along the gum line, which renders the gums and teeth numb: hence the colloquial names of "numbies," or "gummy," for this type of administration. This is commonly done with the small amounts of cocaine remaining on a surface after insufflation. Another oral method is to wrap up some cocaine in rolling paper and swallow it. This is called "parachuting".

Mechanism of action

The pharmacodynamics of cocaine are complex. One significant effect of cocaine on the central nervous system is the blockage of the dopamine transporter protein (DAT), hence cocaine is called a dopamine reuptake inhibitor. Brain regions that are rich with dopaminergic neurons are the ventral tegmental area (VTA), and the substantia nigra (SN). The dopamine (DA) neurons of the VTA send axons to the nucleus accumbens (nAC)and the prefrontal cortex (PFC) and release DA presynaptically on the neurons in these regions. While the precise role of DA in the subjective experience of reward is controversial among neuroscientists, the release of DA in the nAC is widely considered to be responsible for cocaine's rewarding effects. This conclusion is largely based on laboratory data involving rats that are trained to self-administer cocaine intravenously (i.v.). If DA antagonists are infused directly into the nAC, well-trained rats self-administering cocaine will undergo extinction (i.e., initially increase responding only to stop completely) thereby indicating that cocaine is no longer reinforcing (i.e., rewarding) drug-seeking behavior.

A monoamine transmitter by a neuron for signal firing is normally recycled via the transporter to terminate the signal and to spare transmitter resources. The transporter binds the transmitter and pumps it out of the synaptic cleft back into the pre-synaptic neuron. There it is taken up into storage vesicles. Cocaine binds tightly at the DAT forming a

complex that blocks the transporter's function, this also blocks the reuptake of the transmitter. Once released into the extracellular space (synaptic cleft) dopamine accumulates there, because the recycling mechanism is inhibited by the cocaine. This results in an enhanced and prolonged post-synaptic effect of dopaminergic signalling at dopamine receptors on the receiving neuron. Prolonged exposure to cocaine, as occurs with habitual use, leads to homeostatic dysregulation of normal (i.e., without cocaine) dopaminergic signaling via downregulation of D1 receptors and enhanced signal transduction. The decreased dopaminergic signalling after chronic cocaine use may contribute to depressive mood disorders and sensitize this important brain reward circuit to the reinforcing effects of cocaine (e.g., enhanced dopaminergic signalling only when cocaine is self-administered). This sensitization contributes to the intractable nature of addiction and relapse.

Cocaine is also a less potent blocker of the norepinephrine transporter (NET) and serotonin transporter (SERT). Cocaine also blocks sodium channels, thereby interfering with the propagation of action potentials; thus, like lignocaine and novocaine, it acts as a local anesthetic. Cocaine also causes vasoconstriction, thus reducing bleeding during minor surgical procedures. The locomotor enhancing properties of cocaine may be attributable to its enhancement of dopaminergic transmission from the substantia nigra. Recent research points to an important role of circadian mechanisms[18] and clock genes[19] in behavioral actions of cocaine.

Because nicotine increases the levels of dopamine in the brain, many cocaine users find that consumption of tobacco products during cocaine use enhances the euphoria. This, however, may have undesirable consequences, such as uncontrollable chain smoking during cocaine use (even users who don't normally smoke cigarettes have been known to chain smoke when using cocaine), in addition to the detrimental health effects and the additional strain on the cardiovascular system caused by tobacco.

Metabolism and excretion

Cocaine is extensively metabolized, primarily in the liver, with only about 1% excreted unchanged in the urine. The metabolism is dominated by hydrolytic ester cleavage, so the eliminated metabolites consist mostly of benzoylecgonine, the major metabolite, and in lesser amounts ecgonine methyl ester and ecgonine.

If taken with alcohol, cocaine combines with the ethanol in the liver to form cocaethylene, which is both more euphorigenic and has higher cardiovascular toxicity than cocaine by itself.

Cocaine metabolites are detectable in urine for up to four days after cocaine is used. Benzoylecgonine can be detected in urine within four hours after cocaine inhalation and remains detectable in concentrations greater than 1000 ng/ml for as long as 48 hours. Detection in hair is possible in regular users until the sections of hair grown during use are cut or fall out.

Effects and health issues

Acute

Cocaine is a potent central nervous system stimulant. Its effects can last from 20 minutes to several hours, depending upon the dosage of cocaine taken, purity, and method of administration.

The initial signs of stimulation are hyperactivity, restlessness, increased blood pressure, increased heart rate and euphoria. The euphoria is sometimes followed by feelings of discomfort and depression and a craving to experience the drug again. Sexual interest and pleasure can be amplified. Side effects can include twitching, paranoia, and impotence, which usually increases with frequent usage.

With excessive dosage the drug can produce hallucinations, paranoid delusions, tachycardia, itching, and formication.

Overdose causes tachyarrhythmias and a marked elevation of blood pressure. These can be life-threatening, especially if the user has existing cardiac problems.

The LD50 of cocaine when administered to mice is 95.1 mg/kg.[20] Toxicity results in seizures, followed by respiratory and circulatory depression of medullar origin. This may lead to death from respiratory failure, stroke, cerebral hemorrhage, or heart-failure. Cocaine is also highly pyrogenic, because the stimulation and increased muscular activity cause greater heat production. Heat loss is inhibited by the intense vasoconstriction. Cocaine-induced hyperthermia may cause muscle cell destruction and myoglobinuria resulting in renal failure. There is no specific antidote for cocaine overdose.

Cocaine's primary acute effect on brain chemistry is to raise the amount of dopamine and serotonin in the nucleus accumbens (the pleasure center in the brain); this effect ceases, due to metabolism of cocaine to inactive compounds and particularly due to the depletion of the transmitter resources (tachyphylaxis). This can be experienced acutely as feelings of depression, as a "crash" after the initial high. Further mechanisms occur in chronic cocaine use.

Chronic

With chronic cocaine intake, brain cells functionally adapt (respond) to strong imbalances of transmitter levels in order to compensate extremes. So receptors disappear from or reappear on the cell surface, resulting more or less in an "off" or "working mode" respectively, or they change their susceptibility for binding partners (ligands) – mechanisms called down-/upregulation. Chronic cocaine use leads to a DAT upregulation, further contributing to depressed mood states. Finally, a loss of vesicular monoamine transporters, neurofilament proteins, and other morphological changes appear to indicate a long term damage of dopamine neurons.

All these effects contribute to the rise in an abuser's tolerance thus requiring a larger dosage to achieve the same effect. The lack of normal amounts of serotonin and dopamine in the brain is the cause of the dysphoria and depression felt after the initial high. The

diagnostic criteria for cocaine withdrawal is characterized by a dysphoric mood, fatigue, unpleasant dreams, insomnia or hypersomnia, E.D., increased appetite, psychomotor retardation or agitation, and anxiety.

Cocaine abuse also has multiple physical health consequences. It is associated with a lifetime risk of heart attack that is seven times that of non-users. During the hour after cocaine is used, heart attack risk rises 24-fold.

Side effects from chronic smoking of cocaine include chest pain, lung trauma, shortness of breath, sore throat, hoarse voice, dyspnea, and an aching, flu-like syndrome. A common misconception is that the smoking of cocaine chemically breaks down tooth enamel and causes tooth decay. However, cocaine does often cause involuntary tooth grinding, known as bruxism, which can deteriorate tooth enamel and lead to gingivitis.

Chronic intranasal usage can degrade the cartilage separating the nostrils (the septum nasi), leading eventually to its complete disappearance. Due to the absorption of the cocaine from cocaine hydrochloride, the remaining hydrochloride forms a dilute hydrochloric acid.[1]

Cocaine may also greatly increase this risk of developing rare autoimmune or connective tissue diseases such as lupus, Goodpasture's disease, vasculitis, glomerulonephritis, Stevens-Johnson syndrome and other diseases.[21][22][23][24] It can also cause a wide array of kidney diseases and renal failure.[25][26] While these conditions are normally found in chronic use they can also be caused by short term exposure in susceptible individuals.

There have been published studies reporting that cocaine causes changes in the frontal lobe of the brain. The full extent of possible brain deterioration from cocaine use is not known.

Cocaine as a local anesthetic

Cocaine was historically useful as a topical anesthetic in eye and nasal surgery, although it is now predominantly used for nasal and lacrimal duct surgery. The major disadvantages of this use are cocaine's intense vasoconstrictor activity and potential for cardiovascular toxicity. Cocaine has since been largely replaced in Western medicine by synthetic local anaesthetics such as benzocaine, proparacaine, and tetracaine though it remains available for use if specified. If vasoconstriction is desired for a procedure (as it reduces bleeding), the anesthetic is combined with a vasoconstrictor such as phenylephrine or epinephrine. In Australia it is currently prescribed for use as a local anesthetic for conditions such as mouth and lung ulcers. Some Australian ENT specialists occasionally use cocaine within the practice when performing procedures such as nasal cauterization. In this scenario dissolved cocaine is soaked into a ball of cotton wool, which is placed in the nostril for the 10-15 minutes immediately prior to the procedure, thus performing the dual role of both numbing the area to be cauterized and also vasoconstriction.

Cocaine trade

Because of the extensive processing it undergoes during preparation, cocaine is generally treated as a 'hard drug', with severe penalties for possession and trafficking. Demand

remains high, and consequently black market cocaine is quite expensive. Unprocessed cocaine, such as coca leaves, is occasionally bought and sold, but this is exceedingly rare as it is much easier and more profitable to conceal and smuggle it in powdered form.

Production

As of 1999, Colombia was the world's leading producer of cocaine. Three-quarters of the world's annual yield of cocaine was produced there, both from cocaine base imported from Peru (primarily the Huallaga Valley) and Bolivia, and from locally grown coca. There was a 28 percent increase from the amount of potentially harvestable coca plants which were grown in Colombia in 1998. This, combined with crop reductions in Bolivia and Peru, made Colombia the nation with the largest area of coca under cultivation. Coca grown for traditional purposes by indigenous communities, a use which is still present and is permitted by Colombian laws, only makes up a small fragment of total coca production, most of which is used for the illegal drug trade. Attempts to eradicate coca fields through the use of defoliants have devastated part of the farming economy in some coca growing regions of Colombia, and strains appear to have been developed that are more resistant or immune to their use. Whether these strains are natural mutations or the product of human tampering is unclear. These strains have also shown to be more potent than those previously grown, increasing profits for the drug cartels responsible for the exporting of cocaine. The cultivation of coca has become an attractive, and in some cases even necessary, economic decision on the part of many growers due to the combination of several factors, including the persistence of worldwide demand, the lack of other employment alternatives, the lower profitability of alternative crops in official crop substitution programs, the eradication-related damages to non-drug farms, and the spread of new strains of the coca plant.

Estimated Andean Region Coca Cultivation and Potential Pure Cocaine Production, 2000–2004.[27]\

	2000	2001	2002	2003	2004
Net Cultivation (km²)	1875	2218	2007.5	1663	1662
Potential Pure Cocaine Production (tonnes)	770	925	830	680	645

Trafficking and distribution

Organized criminal gangs operating on a large scale dominate the cocaine trade. Most cocaine is grown and processed in South America, particularly in Colombia and Peru, and smuggled into the United States and Europe, where it is sold at huge markups.

Cocaine shipments from South America transported through Mexico or Central America are generally moved over land or by air to staging sites in northern Mexico. The cocaine is then broken down into smaller loads for smuggling across the U.S.–Mexico border. The primary cocaine importation points in the United States are in Arizona, southern California,

southern Florida, and Texas. Typically, land vehicles are driven across the U.S.-Mexico border.

Cocaine is also carried in small, concealed, kilogram quantities across the border by couriers known as “mules” (or “burros”), who cross a border either legally, e.g. through a port or airport, or illegally through undesignated points along the border. The drugs may be strapped to the waist or legs or hidden in bags, or hidden in the body. If the mule gets through without being caught, the gangs will reap most of the profits. If he or she is caught however, gangs will sever all links and the mule will usually stand trial for trafficking by him- or herself.

Cocaine traffickers from Colombia, and recently Mexico, have also established a labyrinth of smuggling routes throughout the Caribbean, the Bahama Island chain, and South Florida. They often hire traffickers from Mexico or the Dominican Republic to transport the drug. The traffickers use a variety of smuggling techniques to transfer their drug to U.S. markets. These include airdrops of 500–700 kg in the Bahama Islands or off the coast of Puerto Rico, mid-ocean boat-to-boat transfers of 500–2,000 kg, and the commercial shipment of tonnes of cocaine through the port of Miami.

Bulk cargo ships are also used to smuggle cocaine to staging sites in the western Caribbean–Gulf of Mexico area. These vessels are typically 150–250 foot (50–80 m) coastal freighters that carry an average cocaine load of approximately 2.5 tonnes. Commercial fishing vessels are also used for smuggling operations. In areas with a high volume of recreational traffic, smugglers use the same types of vessels, such as go-fast boats, as those used by the local populations.

"Black cocaine"

Traffickers have also started using a method whereby a substance such as iron thiocyanate,[1] a mixture of cobalt and ferric chloride,[28] or a mixture of charcoal and iron filings [29] is added to cocaine hydrochloride to produce “black cocaine.” The cocaine in this substance is not detected by standard chemical tests such as the Becton Dickinson test kit. The substance was first identified after a seizure in March 1998 in Germany, which was then tracked back to discover 250 lb of black cocaine ready for transport at Bogotá’s airport. [29]

Addiction

Cocaine addiction is the excessive intake of cocaine, and can result in physiological damage, lethargy, depression, or a potentially fatal overdose. The immediate craving to use more cocaine is strong and very common, because euphoric effects usually subside in most users within an hour of the last dosage, leading to serial cocaine readministrations, and prolonged, multi-dose binge use in those who are addicted. When administration stops after binge use, it is followed by a "crash", the onset of severely dysphoric mood with escalating exhaustion until sleep is achieved. Resumption of use may occur upon awakening or may not occur for several days, but the intense euphoria such use can, as it has in many users, produce intense craving and develop rather quickly into addiction. The risk[30] of becoming cocaine-dependent within 2 years of first use(recent-onset) is 5-6%; after 10 years, it's 15-16%.

These are the aggregate rates for all types of use considered, i.e., smoking, snorting, injecting. Among recent-onset users, the relative rates are higher for smoking (3.4 times) and much higher for injecting (31 times). They also vary, based on other characteristics, such as gender: among recent-onset users, females are 3.3 times more likely to become addicted, compared to males; age: among recent-onset users, those who started using at ages 12 or 13 were 4 times as likely to become addicted, compared to those who started between ages 18 and 20; and race: among recent-onset users, non-Hispanic Blacks are 7 times as likely to become addicted, compared to non-Hispanic Whites. Many habitual abusers develop a transient manic-like condition similar to amphetamine psychosis and schizophrenia, whose symptoms include aggression, severe paranoia, and tactile hallucinations (including the feeling of insects under the skin, or "coke bugs") during binges.[31]

Cocaine has positive reinforcement effects, which refers to the effect that certain stimuli have on behavior. Good feelings become associated with the drug, causing a frequent user to take the drug as a response to bad news or mild depression. This activation strengthens the response that was just made. If the drug was taken by a fast acting route such as injection or inhalation, the response will be the act of taking more cocaine, so the response will be reinforced. Powder cocaine, being a club drug is mostly consumed in the evening and night hours. Because cocaine is a stimulant, a user will often drink large amounts of alcohol during and after usage or smoke cannabis to dull "crash" effects and hasten slumber. Benzodiazepines (e.g., xanax, rohypnol) are also used for this purpose. Other drugs such as heroin and various pharmaceuticals are often used to amplify reinforcement or to minimize such negative effects, further increasing addiction potential and harmfulness.

It has been shown in studies that rhesus monkeys provided with a mechanism of cocaine self-administration prefer the drug over food that is in the cage. This happens even when the monkeys are starving.[32]

It is speculated that cocaine's addictive properties stem partially from its DAT-blocking effects (in particular, increasing the dopaminergic transmission from ventral tegmental area neurons). However, a study has shown that mice with no dopamine transporters still exhibit the rewarding effects of cocaine administration.[33] Later work demonstrated that a combined DAT/SERT knockout eliminated the rewarding effects.[34] The rewarding effects of cocaine are influenced by circadian rhythms,[35] possibly by involving a set of genes termed "clock genes".[36] However, chronic cocaine addiction is not solely due to cocaine reward. Chronic repeated use is needed to produce cocaine-induced changes in brain reward centers and consequent chronic dysphoria (described above under "Effects and Health Issues - Chronic"). Dysphoria magnifies craving for cocaine because cocaine reward rapidly, albeit transiently, improves mood. This contributes to continued use and a self-perpetuating, worsening condition, since those addicted usually cannot appreciate that long-term effects are opposite those occurring immediately after use.

Treatment

Cognitive Behavioral Therapy (CBT) shows promising results. One or more cocaine vaccines exist or are on trial that will stop desirable effects from the drug. The National Institutes of Health of an unspecified country is researching modafinil, a narcolepsy drug and

mild stimulant, as a potential cocaine treatment. Twelve-step programs such as Cocaine Anonymous (modeled on Alcoholics Anonymous) are claimed by many cocaine addicts to be helpful in achieving long-term abstinence. These spiritual programs have no statistically-measurable effect as Alcoholics Anonymous does not release any quantifiable measure of its success rates. There are, however, many recovering addicts who claim this program has aided them.

GVG

Studies have shown that gamma vinyl-gamma-aminobutyric acid (gamma vinyl-GABA, or GVG), a drug normally used to treat epilepsy, blocks cocaine's action in the brains of primates. GVG increases the amount of the neurotransmitter GABA in the brain and reduces the level of dopamine in the region of the brain that is thought to be involved in addiction. In January 2005 the U.S. Food and Drug Administration gave permission for a Phase I clinical trial of GVG for the treatment of addiction. Another drug currently tested for anti-addictive properties is the cannabinoid antagonist rimonabant.

GBR 12909

GBR 12909 (Vanoxerine) is a selective dopamine uptake inhibitor. Because of this, it reduces cocaine's effect on the brain, and may help to treat cocaine addiction. Studies have shown that GBR, when given to primates, suppresses cocaine self-administration.

Venlafaxine

Venlafaxine (Effexor), although not a dopamine re-uptake inhibitor, is a serotonin-norepinephrine reuptake inhibitor that has been successfully used to combat the depression caused by cocaine withdrawal and to a lesser extent, the addiction associated with the drug itself. Venlafaxine has been shown to have significant withdrawal problems itself, and can lead to lifetime use due to these withdrawal effects. A statisically significant number of people prescribed Effexor have committed suicide (2 attempts per 1000 patients, vs 1.56 suicides per 1,000 untreated depressives).

Coca teas

Coca herbal tea has been used for the treatment of cocaine dependence. The effects of the coca tea are a nice stimulation and mood lift. It doesn't produce any significant numbing of the mouth nor does it give a rush like snorting cocaine. Much of the effect of coca seems to come from the secondary alkaloids, as it is not only quantitatively different from pure cocaine but also qualitatively different. In one study, coca tea was used—in addition to counseling—to treat 23 addicted coca-paste smokers in Lima, Peru. Relapses fell from an

average of 4.35 times per month before treatment with coca tea to 1.22 during the treatment. Abstinence length increased from an average of 32 days prior to treatment to 217.2 days during treatment. These results suggest that coca tea is an effective method for preventing relapse during treatment for cocaine addiction.[37]

Legal status

The production, the distribution and the sale of cocaine products is restricted (and illegal in most contexts) in most countries. Since 1914, when The Harrison Narcotics Tax Act passed in the U.S., cocaine has been considered a 'hard drug.' In Colombia, the indigenous population is allowed to grow coca for traditional reasons. All other coca is considered part of the illegal black market. In parts of Africa, it is a crime to be in possession of cocaine or even be seen with it. In South America, cultivation of coca is allowed only with special permission; however, it is a crime to posses processed cocaine. Some parts of Europe and Australia allow processed cocaine for medicinal uses only. Also, in some parts of the Middle East and Asia, being in possession of cocaine can be punishable by death.

Usage

In the United States

Overall usage

In the late 1800's, many authors of this time, including Freud, openly admitted to going on cocaine binges to complete their works. But at the turn of the twentieth century, the dangers of cocaine were becoming apparent and the public did not want a society of drug addicts. There was a public outcry against the use and abuse of cocaine. Groups were demonizing cocaine users as the low-lifes of society. There was also a racial backlash, and many people blamed the African American community.

During the 60's cocaine had become mainstream again, yet it was still illegal. Prices of cocaine began to rise, and those of the lower class could no longer afford their addiction. Cocaine has become the second most popular illegal recreational drug in the U.S.Cocaine is generally used by privileged middle to upper class communities. It is also popular amongst college students, not just to aide in studying, but also as a party drug. Its users span over different ages, races, and professions. In the 1970's and 80's the drug became particularly popular in the disco culture as cocaine usage was very common and popular in many discos such as Studio 54.

The National Household Survey on Drug Abuse (NHSDA) reported in 1999 that cocaine was used by 3.7 million Americans, or 1.7 percent of the household population age 12 and older. Estimates of the current number of those who use cocaine regularly (at least once per month) vary, but 1.5 million is a widely accepted figure within the research community.

Although cocaine use had not significantly changed over the six years prior to 1999, the number of first-time users went up from 574,000 in 1991, to 934,000 in 1998 — an increase of 63%. While these numbers indicated that cocaine is still widely present in the United

States, cocaine use was significantly less prevalent than it was during the early 1980s. Cocaine use peaked in 1982 when 10.4 million Americans (5.6 percent of the population) reportedly used the drug.

Usage among youth

The 1999 Monitoring the Future (MTF) survey found the proportion of American students reporting use of powder cocaine rose during the 1990s. In 1991, 2.3 percent of eighth-graders stated that they had used cocaine in their lifetime. This figure rose to 4.7 percent in 1999. For the older grades, increases began in 1992 and continued through the beginning of 1999. Between those years, lifetime use of cocaine went from 3.3 percent to 7.7 percent for tenth-graders and from 6.1 percent to 9.8 percent for twelfth-graders. Lifetime use of crack cocaine, according to MTF, also increased among eighth-, tenth-, and twelfth-graders, from an average of 2 percent in 1991 to 3.9 percent in 1999.

Perceived risk and disapproval of cocaine and crack use both decreased during the 1990s at all three grade levels. The 1999 NHSDA found the highest rate of monthly cocaine use was for those aged 18–25 at 1.7 percent, an increase from 1.2 percent in 1997. Rates declined between 1996 and 1998 for ages 26–34, while rates slightly increased for the 12–17 and 35+ age groups. Studies also show people are experimenting with cocaine at younger ages. NHSDA found a steady decline in the mean age of first use from 23.6 years in 1992 to 20.6 years in 1998.

Availability

Cocaine is readily available in all major countries' metropolitan areas. According to the Summer 1998 Pulse Check, published by the U.S. Office of National Drug Control Policy, cocaine use had stabilized across the country, with a few increases reported in San Diego, Bridgeport, Miami, and Boston. In the West, cocaine usage was lower, which was thought to be because some users were switching to methamphetamine, which was cheaper and provides a longer-lasting high. Numbers of cocaine users are still very large, with a concentration among city-dwelling youth.

Cocaine is typically sold to users by the gram ($40-$80US) or eight ball (3.5 grams, or roughly 1/8th oz; hence the term "eight ball") ($100-$250). Quality and price can vary dramatically depending on demand and supply.

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See also

- Coca
- Psychoactive drug

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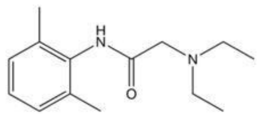
- Adam Gottlieb Pleasures of Cocaine: If You Enjoy: This Book May Save Your Life ISBN 0-914171-81-X (paperback 1996)
- Carol Saline Doctor Snow: How the FBI Nailed a Ivy League Coke King ISBN 0-453-00593-4 (HardCover 1986)
- Mark Bowden Doctor Dealer: The Rise & Fall Of An All American Boy and his Multi-Million Dollar Cocaine Empire ISBN 0-446-51382-2

Lidocaine



Systematic (IUPAC) name

2-(diethylamino)-
N-(2,6-dimethylphenyl)acetamide

Identifiers

CAS number 137-58-6

ATC code N01**BB02** C01**BB01**

PubChem 3676

DrugBank APRD00479

Chemical data

Formula $C_{14}H_{22}N_2O$

Mol. weight 234.34 g/mol

Physical data

Melt. point 68 °C (154 °F)

Pharmacokinetic data

Bioavailability 35% (oral), 3% (topical)

Metabolism hepatic 90% (CYP1A2)

Half life 1.5–2 hours

Excretion renal

Therapeutic considerations

Pregnancy cat. A (Australia)

Legal status Schedule 4 (Australia)

Routes IV, subcutaneous, topical

Lidocaine (INN) (IPA: [Èlajdokejn]) or *lignocaine* (former BAN) (IPA: [Èljgnokejn]) is a common local anesthetic and antiarrhythmic drug. The most commonly encountered lidocaine preparations are marketed by AstraZeneca under the brand names *Xylocaine* and *Xylocard*, though lidocaine is also found in many other proprietary preparations.

History

Lidocaine, the first amino amide-type local anesthetic, was developed by Nils Löfgren and Bengt Lundqvist in 1943 and first marketed in 1948.

Pharmacokinetics

Lidocaine has a more rapid onset of action and longer duration of action than amino ester-type local anesthetics such as procaine. It is approximately 90% metabolized in the liver by CYP1A2 (and to a minor extent CYP3A4) to the pharmacologically-active metabolites monoethylglycinexylidide and glycinexylidide.

The elimination half-life of lidocaine is approximately 1.5–2 hours in most patients. This may be prolonged in patients with hepatic impairment (average 343 minutes) or congestive heart failure (average 136 minutes). (Thomson et al., 1973)

Pharmacology

Anesthesia

Lidocaine alters depolarization in neurons, by blocking the fast sodium (Na^+) channels in the cell membrane. With sufficient blockade, the membrane will not depolarise and so not transmit an action potential, leading to its anesthetic effects.

Antiarrhythmia

Lidocaine is classified as a Class Ib antiarrhythmic agent, blocking the sodium channel of the cardiac action potential, which decreases automaticity by reducing the slope of phase 0 of depolarization with little effect on the PR interval, QRS complex or QT interval.

Clinical use

Indications

Indications for the use of lidocaine include:

- Topical, infiltration, nerve block, ophthalmic, epidural and intrathecal anaesthesia, IV regional anaesthesia (IVRA)
- Treatment of serious ventricular arrhythmias (IV preparations), including VF (Ventricular Fibrillation) associated with cardiac arrest

- Neuropathic pain, including postherpetic neuralgia

Contraindications

Contraindications for the use of lidocaine include:

- Heart block, second or third degree (without pacemaker) Severe sinoatrial block (without pacemaker) Serious adverse drug reaction to lignocaine or amide local anaesthetics Concurrent treatment with quinidine, flecainide, disopyramide, procainamide (Class I antiarrhythmic agents)

Adverse drug reactions

Adverse drug reactions (ADRs) are rare when lidocaine is used as a local anesthetic and is administered correctly. Most ADRs associated with lidocaine for anesthesia relate to administration technique (resulting in systemic exposure) or pharmacological effects of anesthesia, however allergic reactions can rarely occur.

Systemic exposure to excessive quantities of lidocaine mainly result in central nervous system (CNS) and cardiovascular effects – CNS effects usually occur at lower plasma concentrations and additional cardiovascular effects present at higher concentrations, though cardiovascular collapse may also occur with low concentrations. CNS effects may include CNS excitation (nervousness, tingling around the mouth, tinnitus, tremor, dizziness, blurred vision, seizures) followed by depression (drowsiness, loss of consciousness, respiratory depression and apnea). Cardiovascular effects include hypotension, bradycardia, arrhythmias, and/or cardiac arrest – some of which may be due to hypoxemia secondary to respiratory depression. (Rossi, 2006)

ADRs associated with the use of intravenous lidocaine are similar to toxic effects from systemic exposure above. These are dose-related and more frequent at high infusion rates (e3 mg/minute). Common ADRs include: headache, dizziness, drowsiness, confusion, visual disturbances, tinnitus, tremor, and/or paraesthesia. Infrequent ADRs assocaited with the use of lidocaine include: hypotension, bradycardia, arrhythmias, cardiac arrest, muscle twitching, seizures, coma, and/or respiratory depression. (Rossi, 2006)

Dosage forms

Lidocaine, usually in the form of *lidocaine hydrochloride*, is available in various forms including:

- Injected local anesthetic (sometimes combined with
- Dermal patch (sometimes combined with prilocaine)
- Intravenous injection (sometimes combined with
- Intravenous infusion
- Nasal instillation/spray (combined with phenylephrine)
- Oral gel (often referred to as "viscous lidocaine" or abbreviated "lidocaine visc" or "lidocaine hcl visc" in pharmacology)

- Oral liquid
- Topical gel (as with Aloe Vera gels that include Lidocaine)
- Topical liquid

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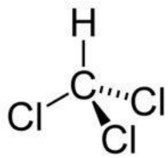
Chloroform

Chloroform



Other names Trichloromethane, Methane trichloride, R-20

Molecular formula CHCl***3***

Molar mass 119.4 g/mol

Appearance colorless liquid

SMILES ClC(Cl)Cl

CAS number [67-66-3]

EINECS number 200-663-8

Properties

Density and phase 1.48 g/cm^3, liquid

Solubility in water 0.8 g/100 ml at 20 °C

Melting point 64 °C

Boiling point 62 °C

Viscosity 0.542 cP at 25 °C

Structure

Molecular shape Tetrahedral

Dipole moment 1.08 D (gas)

Thermodynamic data

Standard enthalpy of formation ”***f***H°***liquid*** 134.3 kJ/mol

Standard enthalpy of formation ″***f***H°***gas*** 103.2 kJ/mol

Standard molar entropy S°***gas*** 295.6 J.K**–1**.mol**–1**

Safety data

EU classification

Harmful

Irritant

Carc. Cat. 3

R-phrases R22, R38, R40 R48/20/22

S-phrases S2, S36/37

PEL-TWA (OSHA) 50 ppm (240 mg/m**3**)

IDLH (NIOSH) approx. 500 ppm

Flash point non-flammable

RTECS number FS9100000

Supplementary data page

Thermodynamic data

Phase behaviour Solid, liquid, gas

Related compounds

Related Haloforms

Fluoroform
Bromoform
Iodoform

Related Chloromethanes

Chloromethane

Dichloromethane

Carbon tetrachloride

Except where noted otherwise, data are given for materials in their standard state (at 25 °C, 100 kPa)

Chloroform, also known as *trichloromethane* and *methyl trichloride*, is a chemical compound with formula $CHCl_3$. It does not support combustion in air, although it will burn when mixed with more flammable substances. It is a member of a subset of environmental pollutants known as *trihalomethanes*, a by-product of chlorination of drinking water and a long-standing health concern.

History

Chloroform was discovered in July, 1831 by American physician Samuel Guthrie (1782-1848), and independently a few months later by French chemist Eugène Soubeiran (1797-1859) and Justus von Liebig (1803-1873) in Germany. Soubeiran produced chloroform through the action of chlorine bleach powder (calcium hypochlorite) upon acetone (propanone) or ethanol (an application of the generic process known as the haloform reaction). Chloroform was named and chemically characterised in 1834 by Jean-Baptiste Dumas (1800-1884). Its anaesthetic properties were noted early in 1847 by Marie-Jean-Pierre Flourens (1794-1867) and Robert James Fegle (1790-1842).

In 1847, the Edinburgh obstetrician James Young Simpson first used chloroform for general anesthesia during childbirth. The use of chloroform during surgery expanded rapidly thereafter in Europe. In the United States, chloroform began to replace ether as an anesthetic at the beginning of the 20th century; however, it was quickly abandoned in favor of ether upon discovery of its toxicity, especially its tendency to cause fatal cardiac arrhythmia analogous to what is now termed "sudden sniffer's death". Ether is still the preferred anesthetic in some developing nations due to its high therapeutic index and low price. Trichloroethylene, a halogenated aliphatic hydrocarbon related to chloroform, was proposed as a safer alternative, though it, too, was later found to be carcinogenic.

Production

Industrially, chloroform is produced by heating a mixture of chlorine and either chloromethane or methane to 400-500°C. At this temperature, a free radical halogenation occurs, converting the methane or chloromethane to progressively more chlorinated compounds.

$CH_4 + Cl_2$ ’ $CH_3Cl + HCl$ $CH_3Cl + Cl_2$ ’ $CH_2Cl_2 + HCl$ $CH_2Cl_2 + Cl_2$ ’ $CHCl_3 + HCl$ $CHCl_3 + Cl_2$ ’ $CCl_4 + HCl$

The output of this process is a mixture of the four chloromethanes, chloromethane, dichloromethane, chloroform (trichloromethane), and carbon tetrachloride, which are then separated by distillation.

The first industrial process was the reaction of acetone (or ethanol) with sodium hypochlorite or calcium hypochlorite. The chloroform can be removed from the resulting sodium acetate or calcium acetate (or sodium formate or calcium formate if ethanol is the starting material) by distillation. The reaction mechanism is called haloform reaction, and is still used for the production of bromoform and iodoform.

This reaction can also occur inadvertently when cleaning around the house. Sodium hypochlorite solution (bleach) and acetone (nail-varnish remover) produces chloroform, sodium hydroxide, sodium acetate, and sodium chloride. There have been reported cases of this method being used in the UK to synthesise chloroform in the home.

Deuterated chloroform is prepared by the reaction of sodium deuteroxide with chloral hydrate. Some of the aldehyde hydrogen is retained in the product, though, and samples of higher isotopic purity are obtained from trichloroacetophenone as starting material.

Uses

In the late 19th and early 20th centuries, chloroform was used as an inhaled anesthetic during surgery. However, safer, more flexible drugs have entirely replaced it in this role. The major use of chloroform today is in the production of the freon refrigerant R-22. However, as the Montreal Protocol takes effect, this use can be expected to decline as R-22 is replaced by refrigerants that are less liable to result in ozone depletion.

Smaller amounts of chloroform are used as a solvent in the pharmaceutical industry and for producing dyes and pesticides. It is used as a solvent for research in academic chemistry laboratories, also. As a solvent it can be used to bond pieces of acrylic glass (which is also known under the trade name 'Perspex'). Chloroform is one of the most effective known solvents for alkaloids in base form, and may be used to extract nitrogenous chemicals from plant material for pharmaceutical processing. It is commercially used to extract morphine from poppies, scopolamine from Datura plants, and so on.

Chloroform reacts with aqueous sodium hydroxide (preferably in the presence of a phase transfer catalyst) to produce dichlorocarbene. This is used to effect ortho-formylation of activated aromatic rings such as phenols, producing aryl aldehydes in a reaction known as the Reimer-Tiemann reaction. Alternatively the carbene may be trapped by an alkene to form a cyclopropane derivative.

Chloroform containing deuterium (heavy hydrogen), $CDCl3$, is the most common solvent used in NMR spectroscopy.

Safety

As might be expected from its use as an anesthetic, inhaling chloroform vapors depresses the central nervous system. Breathing about 900 parts of chloroform per million parts air (900 parts per million) for a short time can cause dizziness, fatigue, and headache. Chronic chloroform exposure may cause damage to the liver (where chloroform is metabolized to phosgene) and to the kidneys, and some people develop sores when the skin is immersed in

chloroform. Approximately 10% of the population has an allergic reaction to chloroform that produces a fever of around 40°C (104°F) upon exposure.

Animal studies have shown that miscarriages occur in rats and mice that have breathed air containing 30 to 300 ppm chloroform during pregnancy and also in rats that have ingested chloroform during pregnancy. Offspring of rats and mice that breathed chloroform during pregnancy have a higher incidence of birth defects, and abnormal sperm have been found in male mice that have breathed air containing 400 ppm chloroform for a few days. The effect of chloroform on reproduction in humans is unknown.

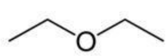
Chloroform once appeared in toothpastes, cough syrups, ointments, and other pharmaceuticals, but it has been banned in consumer products in the United States since 1976.

The NTP's eleventh report on carcinogens implicates it as reasonably anticipated to be a human carcinogen, a designation equivalent to IARC class 2A. It has been most readily associated with hepatocellular carcinoma. Caution is mandated during its handling in order to minimize unnecessary exposure; safer alternatives, such as dichloromethane, have resulted in a substantial reduction of its use as a solvent.

During prolonged storage hazardous amounts of phosgene can accumulate in the presence of oxygen and ultraviolet light. To prevent accidents commercial material is stabilized with ethanol or amylene, but samples that have been recovered or dried no longer contain any stabilizer and caution must be taken with those. Suspicious bottles should be tested for phosgene. Filter paper strips, wetted with 5% diphenylamine, 5% dimethylaminobenzaldehyde, and then dried, turn yellow in phosgene vapor.

Due to its volatile nature, laboratory work with chloroform should be performed under a fume hood to avoid inhaling its fumes. Another problem with its volatility is that it can be difficult to pipette.

Diethyl ether



Systematic name ethoxyethane

Other names diethyl ether, ethyl ether, ethyl oxide

Molecular formula $C_4H_{10}O$ $C_2H_5OC_2H_5$

SMILES CCOCC

Molar mass 74.12 g/mol

Appearance clear, colorless liquid

CAS number [60-29-7]

Properties

Density and phase 0.7134 g/cm3, liquid

Solubility in water 6.9 g/100 ml (20 °C)

Melting point 116.3 °C (156.85 K)

Boiling point 34.6 °C (307.75 K)

Viscosity 0.224 cP at 25 °C

Structure

Dipole moment 1.15 D (gas)

Hazards

MSDS External MSDS

Main hazards Extremely Flammable (F+), Irritant (Xi)
Flash point -45 °C

Autoignition temperature 170 °C

R/S statement ***R12 R19 R22 R66 R67 S9 S16 S29 S33***

RTECS number KI5775000

Related compounds

Related Ethers dimethyl ether

Except where noted otherwise, data are given for materials in their standard state (at 25 °C, 100 kPa)

Diethyl ether, also known as *ether* and *ethoxyethane*, is a clear, colorless, and highly flammable liquid with a low boiling point and a characteristic smell. Diethyl ether has the formula CH_3-CH_2-O-CH_2-CH_3. It is used as a common solvent and has been used as a general anesthetic. Diethyl ether has a high cetane number of 85 - 96 and is used as a starting fluid for diesel and gasoline engines. Ether is sparingly soluble in water (7 g/100 ml).

History

Alchemist Raymundus Lullus is credited with discovering the compound in 1275, although there is no contemporary evidence of this. It was first synthesized in 1540 by

Valerius Cordus, who called it "*oil of sweet vitriol*" (*oleum dulci vitrioli*)—the name was due to the fact that it was originally discovered by distilling a mixture of ethanol and sulfuric acid (then known as oil of vitriol)—and noted some of its medicinal properties. At about the same time, Theophrastus Bombastus von Hohenheim, better known as Paracelsus, discovered ether's analgesic properties. The name ether was given to the substance in 1730 by A.S.Frobenius.

Anesthetic use

The American doctor Crawford Williamson Long, M.D., was the first surgeon to use it as a general anesthetic, on March 30, 1842. William T.G. Morton is credited with the first public demonstration of ether anesthesia on October 16, 1846 at the Ether Dome in Boston, Massachusetts. The use of flammable ether waned as nonflammable anesthetic agents such as halothane became available.

Because of its high volatility, low ignition point, and tendency to form explosive peroxides, diethyl ether must be used with care in laboratory settings.

Ether may be used to anesthetize ticks before removing them from an animal or a person's body. The anesthesia relaxes the tick and prevents it from maintaining its mouthpart under the skin.

Recreational use

The anesthetic effects of ether have made it a recreational drug, although not a popular one. Diethyl ether is not as toxic as other solvents used as recreational drugs.

Ether, mixed with ethanol, was marketed in the 19th century as a cure-all and recreational drug, during one of Western society's temperance movements. At the time, it was considered improper for women to consume alcoholic beverages at social functions, and sometimes ether-containing drugs would be consumed instead. A cough medicine called Hoffmann's Drops was marketed at the time as one of these drugs, and contained both ether and alcohol in its capsules. [1] Ether tends to be difficult to consume alone, and thus was often mixed with drugs like ethanol for recreational use. Ethyl ether is listed as a Table II precursor under the United Nations Convention Against Illicit Traffic in Narcotic Drugs and Psychotropic Substances[2].

Due to its immiscibility with water and the fact that non-polar organic compounds are highly soluble in it, Ether is also used in the production of freebase cocaine.

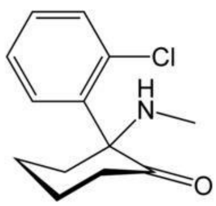
Precautions

Diethyl ether is highly flammable. Its vapors are denser than air and will accumulate if proper ventilation is not present. Simple static electricity will ignite ether vapors. Diethyl ether vapors ignite explosively, and should only be used inside a fume hood.

Additionally, diethyl ether is prone to peroxide formation, and can form explosive diethyl ether peroxide. Ether peroxides are higher boiling and are contact explosives when dry. Ether should never be distilled to dryness, as the risk of explosion increases dramatically. Diethyl ether is typically supplied with BHT (2,6-di-tert-butyl-4-methylphenol), which

reduces the formation of peroxides. Bottles older than 3 months should be routinely tested for peroxides. An iron wire, releasing Fe(III) ions catalyzing the peroxide decomposition, was often added to bottles with diethyl ether as a preventive measure, however, Fe(III) ions also strongly enhance peroxide formation. Storage over NaOH precipitates the intermediate ether hydroperoxides.

Ketamine



Systematic (IUPAC) name

2-(2-chlorophenyl)-2-methylamino-cyclohexan-1-one

Identifiers

CAS number 6740-88-1

ATC code N01**AX03** N01**AX14**

PubChem 3821

DrugBank APRD00493

Chemical data

Formula $C_{13}H_{16}NClO$

Mol. weight 237.725 g/mol

Pharmacokinetic data

Half life 2.5-3 hours.

Excretion renal (>90%)

Therapeutic considerations

Pregnancy cat. B

Legal status Schedule I(CA) Class C(UK) Schedule III(US)

Routes IV, IM, Insufflated, oral, topical

For the collaborative acoustic project, see Katamine.

Ketamine is a general dissociative anaesthetic for human and veterinary use. Its hydrochloride salt is sold as *Ketanest*®, *Ketaset*®, and *Ketalar*®. Pharmacologically it is very similar to other dissociative anesthetics such as tiletamine, memantine and phencyclidine (PCP). As with many other pharmaceuticals, ketamine is used extramedically as a recreational drug.

Ketamine is a chiral compound, with two distinct enantiomers. Most pharmaceutical ketamine preparations are racemic, however reportedly some brands have (mostly undocumented) differences in enantiomeric proportions.

History

Ketamine was first synthesized in 1962 in an attempt to find a safer anaesthetic alternative to Phencyclidine (PCP), which was more likely to cause hallucinations and seizures. The drug was first given to American soldiers during the Vietnam War, but today in the developed world its use on humans has been dramatically curtailed because of exaggerated concern about its potential to cause emergence phenomena including out of body experiences in clinical practice. However, it is still used widely in veterinary medicine, or as a battlefield anesthetic in developing nations.

Ketamine's side effects eventually made it a popular psychedelic in 1965. The drug was used in psychiatric and other academic research through the 1970s, culminating in 1978 with the publishing of John Lilly's The Scientist, a book documenting the author's ketamine, LSD, and isolation tank experiments. The incidence of recreational ketamine use increased through the end of the century, especially in the context of raves and other parties. The increase in illicit use prompted ketamine's placement in Schedule III of the United States Controlled Substance Act in August 1999. In the United Kingdom, it became outlawed and labelled a Class C drug on January 1, 2006.[1] In Canada, as of August 31, 2005, ketamine is classified as a Schedule III narcotic.

Medical use

10 ml bottles of Ketamine *Indicated for:*

Pain relief, surgical anaesthesia
Recreational uses:

Dissociative

psychedelic
Contraindications:

Alcohol

Other **sedatives**

Stimulants

Side effects:

Severe: Impairs all senses, especially:

Sight
Balance
Sense of time
Cardiovascular:
Partial depressant
Gastrointestinal:
Nausea
Musculoskeletal:
Relaxant
Neurological:

Analgesia

Respiratory:
Partial depressant/stimulant

Since it suppresses breathing much less than most other available anaesthetics, ketamine is still used in human medicine as a first-choice anaesthetic for victims with unknown medical history (e.g. from traffic accidents), in podiatry and other minor surgery, and occasionally for the treatment of migraine. There is ongoing research in France, Russia, and the U.S. into the drug's usefulness in pain therapy, depression suppression, and for the treatment of alcoholism and heroin addiction. In veterinary medicine, ketamine is often used for its anaesthetic and analgesic effects on cats, dogs, rabbits, rats, and other small animals. Veterinarians often use ketamine with sedative drugs to produce balanced anaesthesia and analgesia, and as a constant rate infusion to help prevent pain wind-up. Ketamine is used to manage pain among horses and other large animals, though it has less effect on bovines.

Ketamine may be used in small doses (0.1–0.5 mg/kg/h) as an analgesic, particularly for the treatment of pain associated with movement and neuropathic pain. It has the added benefit of counter-acting spinal sensitization or wind-up phenomena experienced with chronic pain. At these doses, the psychotropic side effects are less apparent and well managed with benzodiazepines. Ketamine is a co-analgesic, requiring a concomitant low-dose opioid to be effective.

The effect of Ketamine as a depressant on the respiratory and circulatory systems is less than that of other anaesthetics. When used at anaesthetic doses, it will sometimes stimulate rather than depress the circulatory system. It is sometimes possible to perform ketamine anaesthesia without protective measures to the airways. Ketamine is also a potent analgesic and can be used in sub-anaesthetic doses to relieve acute pain; however, its psychotropic properties must be taken into account. Patients have reported vivid hallucinations, "going into other worlds" or "seeing God" while anaesthetized, and these unwanted psychological side-effects have reduced the use of ketamine in human medicine.

Experimental Antidepressant Use

The National Institute of Health News reports that a study of 17 patients led by Dr Carlos Zarate Jr. of the National Institute of Mental Health found that ketamine significantly improved treatment-resistant major depression within hours of injection. [1] The improvement lasted up to one week after the single dose. [2] The patients in the study were previously treatment resistant, having tried an average of six other treatments that failed. The importance of these findings was articulated by NIMH director Dr Thomas Insel: "To my knowledge, this is the first report of any medication or other treatment that results in such a pronounced, rapid, prolonged response with a single dose. These were very treatment-resistant patients." The researchers apparently attribute the effect to ketamine being an NMDA receptor antagonist. The study appears in the Archives of General Psychiatry. [3] Those findings of Zarate et al corroborate earlier findings by Berman et all. [4]

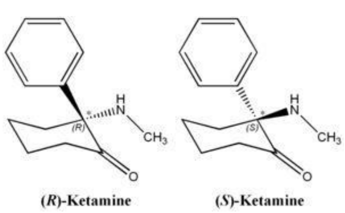
Treatment of addiction

The Russian doctor Evgeny Krupitsky (who is Clinical Director of Research for the Saint Petersburg Regional Center for Research in Addiction and Psychopharmacology) has gained encouraging results by using ketamine as part of a treatment for alcohol addiction which combines psychedelic and aversive techniques [5]. This method involved psychotherapy, controlled ketamine use and group therapy, and resulted in 60 of the 86 alcoholic males selected for the study remaining fully abstinent. He has also treated heroin addicts and reached the conclusion that ketamine reduces the craving for heroin without any adverse reaction [6].

Neuropharmacology

Ketamine, like Phencyclidine, is primarily a non-competitive antagonist of the NMDA receptor, which opens in response to binding of the neurotransmitter glutamate. This NMDA receptor mediates the analgesic (reduction of pain) effects of ketamine at low doses. Evidence for this is reinforced by the fact that naloxone, an opioid antagonist, does not reverse the analgesia. Studies also seem to indicate that ketamine is 'use dependent' meaning it only initiates its blocking action once a glutamate binds to the NMDA receptor.

At high, fully anesthetic level doses, ketamine has also been found to bind to opioid mu receptors and sigma receptors. Thus, loss of consciousness that occurs at high doses may be partially due to binding at the opioid mu and sigma receptors.



Ketamine stereochemistry

Ketamine is racemic, and its R and S stereoisomers have different binding affinities: (S)-Ketamine has about four times greater affinity for the PCP site of the NDMA receptor than

does (R)-Ketamine (in guinea pig brain). The S form also seems to be better at inducing the drowsiness than the R form.[2]

The effects seem to take place mainly in the hippocampal formation and in the prefrontal cortex. This evidence, along with the NMDA receptor's connection with the memory formation process, explains ketamine's profound effects on memory and thought. These effects inhibit the filtering function of the brain and may mirror the sensory overload associated with schizophrenia and near death experiences.

Recreational use

Illicit sale

Ketamine sold illicitly comes from diverted legitimate supplies or theft, primarily veterinary clinics. In the US near its border with Mexico, the drug is most commonly acquired in Mexico, where it can be bought over the counter in veterinary clinics, and smuggled across the border.

In 2003, Operation TKO was a probe conducted by the U.S. Drug Enforcement Agency (DEA). As a result of operation TKO, U.S. and Mexican authorities shut down the Mexico City company, Laboratorios Ttokkyo, which was the biggest producer of ketamine in Mexico. According to the DEA, over 80% of ketamine found in the U.S. is of Mexican origin.[3]

Methods of use

Ketamine is sold in either powdered or liquid form. In powdered form, its appearance is similar to that of pharmaceutical grade cocaine and can be insufflated (snorted, also known as "taking bumps"), injected, or placed in beverages. It is also possible to smoke the drug in a joint or pipe, usually mixed with marijuana and tobacco. The smoke has a distinctive bitter taste but the effects of the high hit much faster than when insufflated or ingested. Oral use usually requires more material, but results in a longer trip. The liquid can be heated to drive off the solvent (usually saline), leaving powder. In therapeutic and psychedelic use, the liquid is typically injected intramuscularly. Intravenous injection is uncommon (recreationally), though possible. It is essentially identical in effect to intramuscular injection, but leads to a much quicker onset — usually within 10 to 15 seconds of dosing. Additionally, intravenous injection tends to lead to a more sudden and marked respiratory depression, especially if the solution is injected at too high of a potency (too fast). These factors make intravenous self-injection dangerous.

Some drug users' first contact with ketamine is accidental, from a pill sold as something else (commonly ecstasy). Ketamine is also commonly combined with other drugs to enhance their effects. There have been claims that ketamine has been used as a date rape drug because of its powerful dissociative effects.

Psychological effects

Unlike true psychedelics, ketamine is powerfully reinforcing to many users and compulsive use is frequently reported. Both ketamine pioneer John Lilly and pseudonymous author D.M. Turner reported prolonged periods of 'ketamine dependency', and the latter drowned in a bathtub while on ketamine.

Ketamine produces effects similar to PCP and DXM. Like other dissociative anesthetics in low- to upper-middle dosages, its hallucinogenic effects are only seen against a background lacking sensory stimulation, such as darkness. Some users claim that a trip due to ketamine use is as good or better than that of PCP or LSD because its overt hallucinatory effects are short-acting, lasting an hour or less in most cases. Effects on the senses, judgment, and coordination, however, can last for 18 to 24 hours. Standing up and moving may be more dangerous than lying still in one place.

Like the other dissociative anaesthetics DXM and PCP, hallucinations caused by ketamine are fundamentally different from those caused by tryptamines and phenethylamines. At low doses hallucinations are only seen when one is in a dark room with one's eyes closed, while at medium to high doses the effects are far more intense and obvious. These effects include changes in the perception of distances and durations as well as a slowing of the visual system's ability to update what the user is seeing. There are reports of high-dosage users being able to see their surroundings in two sharp images, as if the brain is unable to merge the images each eye is sending. Speech often sounds unintelligible and auditory hallucinations may occur.

Ketamine puts the user in a dissociated state, meaning that they are less connected to both a sense of self and the reality around them. If a large enough amount is taken, the user may go into or through a "K-hole", a state of wildly dissociated experience in which other worlds or dimensions that are difficult to describe with language are said to be perceived, all the while being completely unaware of one's individual identity or the outside world. A user may feel as though his or her perception is located so deep inside the mind that the real world seems distant (hence the use of a "hole" to describe the experience). Some users may not remember this part of the experience after regaining consciousness, in the same way that a person may forget a dream. The "re-integration" process is slow, and the user gradually becomes aware of surroundings. At first, a user may not remember his or her own name, or even know that they are human, or what that means. Movement is extremely difficult, and a user may not be aware that they have a body at all.

Ketamine in the media

- In the seventh episode of the first season of the American television series The Dead Zone, titled "Enemy Mind," the lead character, psychic Johnny Smith, accidentally inhales Ketamine in aerosol state, and the drug wreaks havoc with his "dead zone," the primary brain center for his psychic visions.
- In the last episode of the second season of the American televison series House, titled "No Reason," the lead character, Dr. Gregory House, is administered Ketamine to try to relieve the terrible leg pain he has been suffering throughout the course of the series. At the beginning of the third season, it seems that the

Ketamine treatment has worked, though by the end of the second episode his pain has returned and he has started using a walking cane and Vicodin again.

- In the sixth episode of the second season of I'm Alan Partridge, entitled "Alan Wide Shut", Alan Partridge attends a radio interview on a program called Prayer Wave to promote his autobiography and has a surreal, barbed conversation with a woman called Kate Fitzgerald who is also promoting her autobiography. They discuss her ketamine use and move on to talk about Alan's addiction to chocolate, specifically Toblerone.
- In the South Park episode Stupid Spoiled Whore Video Playset (referring to Paris Hilton), the girls say they are going to a party to do Ketamine and then make fun of Wendy for knowing what Ketamine is, saying they have no idea but are going to do it anyway. It is also referred to in the episode You Got F*cked in the Ass where Stan and Chef go to recruit a duck in their dance team. The owner plays two songs for the duck to dance to which contains the line "You do a line and i'll do a line honey" followed by "You snort K and I'll snort K honey".
- Both these South Park episodes have been sampled by STITCH for trax on the BAD SEKTA record label.
- PHUQ released a cdep for BAD SEKTA titled "K Musick [volume one]". His next release is titled "When You Gave Me That Powder You Changed My Life".
- Ketamine is featured also in the episode 44 of the HBO tv-series Six Feet Under, where Russell, one of the students in Claire's art school, reports his experiences after a lengthy trip.
- The band Placebo has a song titled Special K, the content of which is based on the singer's supposed experienced with the drug.
- Ricardo Villalobos, a popular electronic musician affiliated with the microhouse movement, began a unique form of microhouse which eventually came to be called ketamine house.
- Chemical Brothers have a song titled Lost in the K-Hole on their Dig Your Own Hole album.
- The Californian punk band NOFX have a song titled 'Kids of the K Hole' on their 1997 album *So Long and Thanks for All the Shoes*
- CocoRosie, the indie/psych-folk sister duet, has a song called 'K-Hole' on their 2005 album *Noah's Ark* on Touch and Go Records.
- The indie rock group Silver Jews have a song titled 'K-Hole' on their 2005 album *Tanglewood Numbers*.
- The indie pop group The Clientele have songs titled 'Since K Got Over Me' and 'K' on their 2005 album *Strange Geometry*.
- In the movie Cecil B. DeMented, the drug addict character, Lyle, runs in place and shouts "Help! Cherish! I'm stuck in a K-Hole and I can't get out!".
- In the movie Party Monster, starring Macauly Culkin and Seth Green, ketamine was a large part of the main protagonists' downfall.
- In the movie Children of Men, when Julian is talking about when she and Theodore went out to have coffee she refers that his cup was full of ketamine.

- Rock singer Marilyn Manson claims that the experience that resulted from his accidental use of Ketamine (which he mistook for cocaine) inspired the appropriately titled song, 'Disassociative' (from his Mechanical Animals album).

Street Slang

- K
- Ket
- D-rod
- Special K
- Vitamin K
- Lady K
- Spangle
- Big K
- Horsey P

- **See more on** Erowid.org's Ketamine vault

References

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2. ^ **Khamsi, R.** "Ketamine relieves depression within hours" *New Scientist*, **08 August 2006.**

3. ^ Zarate CA Jr, Singh JB, Carlson PJ, Brutsche NE, Ameli R, Luckenbaugh DA, Charney DS, Manji HK. "A randomized trial of an N-methyl-D-aspartate antagonist in treatment-resistant major depression" Archives of General Psychiatry, 2006 Aug;63(8):856-64. PMID 16894061.

4. ^ Berman RM, Cappiello A, Anand A, Oren DA, Heninger GR, Charney DS, Krystal JH. "Antidepressant effects of ketamine in depressed patients". Biol Psychiatry. 2000 Feb 15;47(4):351-4. PMID 10686270.

5. ^ http://www.eleusis.us/resource-center/references/acamethod.php

6. ^ http://www.eleusis.us/resource-center/references/ketamine-psychotherapy-heroin.pdf

See also

- Psychedelics, dissociatives and deliriants

- PCP

- Nitrous oxide
- Dextromethorphan
- Psychoactive drug

Nitrous oxide

Nitrous oxide

Molecular formula N_2O

Molar mass 44.0128 g/mol

Appearance colourless gas

CAS number [10024-97-2]

Properties

Density and phase 1.2 kg m**3** (liquid)

Melting point 90.86 °C (182.29 K)

Boiling point 88.48 °C (184.67 K)

Structure

Molecular shape linear

Dipole moment 0.166 D

Thermodynamic data

Std enthalpy of formation ”***f***Ho***298*** +82.05 kJ/mol

Hazards

MSDS External MSDS

EU classification Oxidising (*O*)
R-phrases **R8**

S-phrases **S38**

Related compounds

Related nitrogen oxides

Nitric oxide
Nitrogen dioxide
Dinitrogen trioxide
Dinitrogen tetroxide
Dinitrogen pentoxide
Nitric acid
Nitrous acid

Related compounds

Nitric acid
Nitrous acid

Except where noted otherwise, data are given for materials in their standard state (at 25 °C, 100 kPa)

Nitrous oxide, also known as *dinitrogen oxide* or *dinitrogen monoxide*, is a chemical compound with chemical formula N2O. Under room conditions, it is a colourless non-flammable gas, with a pleasant, slightly-sweet odor. It is used in surgery and dentistry for its anaesthetic and analgesic effects, where it is commonly known as *laughing gas* due to the euphoric effects of inhaling it. It is also used as an oxidizer in internal combustion engines. In this use it is known as *nitrous*, or *NOS* after a well-known brand which has become a genericized trademark. Nitrous oxide is present in the atmosphere where it acts as a powerful greenhouse gas.

Chemistry

The structure of the nitrous oxide molecule is a linear chain of a nitrogen atom bound to a second nitrogen atom, which in turn is bound to an oxygen atom. It can be considered a resonance hybrid of *NaN***+***O* and *N=N***+***=O*.

Nitrous oxide, N***2***O, should not be confused with the other oxides of nitrogen such as nitric oxide NO and nitrogen dioxide NO***2***.

Nitrous oxide is isoelectronic with carbon dioxide.

It can be prepared by heating ammonium nitrate in the laboratory and can be used to produce nitrites by mixing it with boiling alkali metals, and to oxidize organic compounds at high temperatures.

The CAS number of nitrous oxide is 10024-97-2 and its UN number is 1070.

History

The gas was discovered by Joseph Priestley in 1772, who called it phlogisticated nitrous air (see phlogiston). Humphry Davy in the 1790s tested the gas on himself and some of his friends, including the poets Samuel Taylor Coleridge and Robert Southey. They soon realised that nitrous oxide considerably dulled the sensation of pain, even if the inhaler were still semi-conscious. And so it came into use as an anaesthetic, particularly by dentists, who do not typically have access to the services of an anesthesiologist and who may benefit from a patient who can respond to verbal commands.

Manufacture

Nitrous oxide is most commonly made by fusing and "boiling" ammonium nitrate to form steam, nitrous oxide, nitrogen, ammonium nitrate 'fog' and small amounts of very toxic higher oxides of nitrogen; (NO_2, NO, etc):

NH_4NO_3 ’ N_2O + $2H_2O$, ”H = 36.8 kJ:

The addition of various phosphates favors formation of a purer gas. This reaction occurs at around 240 °C, a temperature where ammonium nitrate is a moderately sensitive explosive and a very powerful oxidizer (perhaps on the order of fuming nitric acid). At temperatures much above 240 °C the exothermic reaction may run away, perhaps up to the point of detonation. The mixture must be cooled to avoid such a disaster. In practice, the reaction involves a series of tedious adjustments to control the temperature to within a narrow range, which it will not naturally tend to stay in. Professionals have destroyed whole neighborhoods by losing control of such commercial processes. Examples include the Ohio Chemical debacle in Montreal, 1966 and the Air Products & Chemicals, Inc. disaster in Delaware City, Delaware, 1977.

The direct oxidation of ammonia may someday rival the ammonium nitrate pyrolysis synthesis of nitrous oxide mentioned above. This capital-intensive process, which originates in Japan, uses a manganese dioxide-bismuth oxide catalyst. (Suwa et al. 1961; Showa Denka Ltd.)

$2NH_3$ + $2O_2$ ’ N_2O + $3H_2O$:

Higher oxides of nitrogen are formed as impurities. Note that uncatalyzed ammonia oxidation (i.e. combustion or explosion) goes primarily to N2 and H2O. The Ostwald process oxidizes ammonia to nitric oxide (NO), using platinum; this is the beginning of the modern synthesis of nitric acid from ammonia (see above).

Nitrous oxide can be made by heating a solution of sulfamic acids and nitric acids. A lot of gas was made this way in Bulgaria (Brozadzhiew & Rettos, 1975).

HNO_3 + NH_2SO_3H ’ N_2O + H_2SO_4 + H_2O:

There is no explosive hazard in this reaction if the mixing rate is controlled. However, as usual, toxic higher oxides of nitrogen form.

Colorless solutions of hydroxylamine hydrochloride and sodium nitrite may also be used to produce N_2O.

$(NH_3OH+Cl-) + NaNO_2$ ’ $N_2O + NaCl + H_2O$:

If the nitrite is added to the hydroxylamine solution, the gas produced is pure enough for inhalation, and the only remaining byproduct is salt water. However, if the hydroxylamine solution is added to the nitrite solution (nitrite is in excess), then toxic higher oxides of nitrogen form are produced.

Uses

Inhalant effects — laughing gas

Nitrous oxide (N_2O) is a dissociative that can cause analgesia, euphoria, dizziness, flanging of sound, and, in some cases, slight hallucinations and mild aphrodisiac effect.

Aerosol propellant

The gas is licensed for use as a food additive (also known as E942), specifically as an aerosol spray propellant. Its most common uses in this context are in aerosol whipped cream canisters and as an inert gas used to displace staleness-inducing oxygen when filling packages of potato chips and other similar snack foods.

The gas is extremely soluble in fatty compounds. In aerosol whipped cream, it is dissolved in the fatty cream until it leaves the can, when it becomes gaseous and thus creates foam. Used in this way, it produces whipped cream four times the volume of the liquid, whereas whipping air into cream only produces twice the volume. If air were used as a propellant, under increased pressure the oxygen would accelerate rancidification of the butterfat, while nitrous oxide inhibits such degradation.

Rocket motors

Nitrous oxide can be used as an oxidizer in a rocket engine. This has the advantages over other oxidizers that it is non-toxic and, due to its stability at room temperature, easy to store and relatively safe to carry on a flight.

Nitrous oxide has been the oxidizer of choice in several hybrid rocket designs (using solid fuel with a liquid or gaseous oxidizer). The combination of nitrous oxide with hydroxyl-terminated polybutadiene fuel has been used by SpaceShipOne and others. It is also notably used in amateur and high power rocketry with various plastics as the fuel. An episode of MythBusters featured a hybrid rocket built using a paraffin/powdered carbon mixture (and later salami) as its solid fuel and nitrous oxide as its oxidizer.

Nitrous oxide can also be used in a monopropellant rocket. In the presence of a heated catalyst, N2O will decompose exothermically into nitrogen and oxygen, at a temperature of approximately 1300° Celsius. In a vacuum thruster, this can provide a monopropellant specific impulse (Isp) of as much as 180s. While noticeably less than the Isp available from hydrazine thrusters (monopropellant or bipropellant with nitrogen tetroxide), the decreased toxicity makes nitrous oxide an option worth investigating.

Internal combustion engine

In racing, nitrous oxide (often just "nitrous" in this context) is sometimes injected into the intake manifold (or prior to the intake manifold; some systems directly inject it into the cylinder) to increase power: even though the gas itself is not flammable, it delivers more oxygen than atmospheric air by breaking down at elevated temperatures, thus allowing the engine to burn more fuel and air. Additionally, since nitrous oxide is stored as a liquid, the evaporation of liquid nitrous oxide in the intake manifold causes a large drop in intake charge temperature. This results in a denser charge, and can reduce detonation, as well as increase power available to the engine.

The same technique was used during by World War II Luftwaffe aircraft with the GM 1 system to boost the power output of aircraft engines. Originally meant to provide the Luftwaffe standard aircraft with superior high-altitude performance, technological considerations limited its use to extremely high altitudes. Accordingly, it was only used by specialized planes like high-altitude reconnaissance aircraft, high-speed bombers and high-altitude interceptors.

One of the major problems of using nitrous oxide in a reciprocating engine is that it can produce enough power to destroy the engine. Power increases of 100–300% are possible, and unless the mechanical structure of the engine is reinforced, the engine may not survive this kind of operation.

It is very important with nitrous oxide augmentation of internal combustion engines to maintain temperatures and fuel levels so as to prevent preignition, or detonation (sometimes referred to as knocking or pinging).

Safety

The major safety hazards of nitrous oxide come from the fact that it is a compressed liquified gas, and a dissociative anaesthetic.

While normally inert in storage and fairly safe to handle, nitrous oxide can decompose energetically and potentially detonate if initiated under the wrong circumstances. Liquid nitrous oxide acts as a good solvent for many organic compounds; liquid mixtures can form somewhat sensitive explosives. Contamination with fuels has been implicated in a handful of rocketry accidents, where small quantities of nitrous / fuel mixtures detonated, triggering the explosive decomposition of residual nitrous oxide in plumbing.

Nitrous oxide in an atmosphere

Unlike the other Nitrogen oxides, nitrous oxide is a major greenhouse gas; per unit of weight, nitrous oxide has 296 times the effect of carbon dioxide (CO2) for producing global warming. Nitrous oxide is thus part of efforts to curb greenhouse gas emissions, such as the Kyoto Protocol. Behind carbon dioxide and methane, which has 23 times the greenhouse warming potential of carbon dioxide (over 100 years), nitrous oxide is the third most important gas that contributes to global warming. (The other nitrogen oxides contribute to

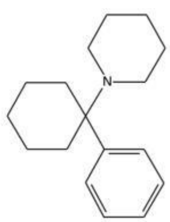
global warming indirectly, by contributing to tropospheric ozone production during smog formation).

Nitrous oxide also attacks ozone in the stratosphere, aggravating the excess amount of UV striking the earth's surface in recent decades (various freons and related halogenated organics also consume ozone in the stratosphere). In the pre-industrial atmosphere nitrous oxide was (and remains) the main natural regulator of stratospheric ozone.

Nitrous oxide is naturally emitted by bacteria in soils and oceans. Agriculture is the main source of human-produced nitrous oxide: cultivating soil, the use of nitrogen fertilizers, and animal waste handling can all stimulate naturally occurring bacteria to produce more nitrous oxide. Industrial sources make up only about 20% of all anthropogenic sources, and include the production of nylon and nitric acid and the burning of fossil fuel in internal combustion engines.

Human activity is thought to account for somewhat less than 2 teragrams (this is multiplied by about 300 when calculated as a ratio to carbon dioxide) of nitrogen oxides per year, nature for over 15 teragram. The global anthropogenic nitrous oxide flux is about 1 petagram of carbon dioxide carbon-equivalents per year; this compares to 2 petagrams of methane carbon dioxide carbon-equivalents per year, and to an atmospheric loading rate of about 3.3 petagrams of carbon dioxide carbon-equivalents per year.

Phencyclidine



Chemical formula $C_{17}H_{25}N$

Molar mass 243.387 g mol1

Systematic name 1-(1-phenylcyclohexyl)piperidine

Phencyclidine (a contraction of the chemical name phenylcyclohexylpiperidine), abbreviated *PCP*, is a dissociative drug formerly used as an anesthetic agent, exhibiting hallucinogenic and neurotoxic effects.

PCP was commercially developed in the 1950s by the Parke-Davis pharmaceutical company. PCP is listed as a Schedule II drug in the United States under the Convention on Psychotropic Substances.[1]

Chemistry and pharmacology

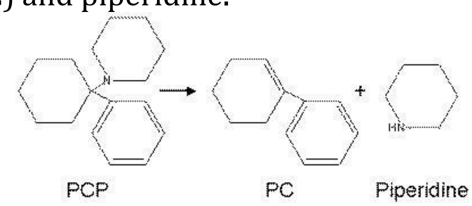
Chemically and pharmacologically it is a member of the family of dissociative anesthetics, which also includes ketamine, tiletamine and high doses of dextromethorphan. Although the primary psychoactive effects of the drug only last hours, total elimination from the body is prolonged, typically extending over weeks.

Toxicology

PCP is a neurotoxin. It is more toxic than other dissociatives and its toxicity is more complex. The damages concern different brain regions and probably affect diverse receptor systems.[2] [3]

Medical and veterinary use

PCP was first tested after World War I as a surgical anaesthetic. Because of its adverse side-effects, it was shelved until the 1950s. It was then patented by Parke-Davis and named Sernyl (supposedly referring to serenity), but was again withdrawn from the market because of side effects. It was soon renamed Sernylan, and marketed as a veterinary anaesthetic, but again discontinued. Its side effects and long half-life in the human body made it unsuitable for medical applications. It is retained in fatty tissue and is broken down by the human metabolism into PCHP, PPC and PCAA. When smoked, some of it is broken down by heat into 1-phenyl-1-cyclohexene (PC) and piperidine.



Recreational use

PCP is consumed recreationally, mainly in the United States[citation needed], where the demand is met by illegal production. The drug is sold in an extremely limited number of cities, such as Washington, DC and Los Angeles[citation needed]. It is available as a liquid (PCP base dissolved most often in ether), but typically it is sprayed onto leafy material such as marijuana, mint, oregano, parsley or Ginger Leaves, and smoked. It is sometimes taken with Ecstasy -- a practice known as "Elephant flipping". PCP is a Schedule II substance in the United States and a Class A substance in Great Britain.

Biochemical action

The N-methyl-D-Aspartate (NMDA) receptor, a type of ionotropic receptor, is found on the dendrites of neurons and receives signals in the form of neurotransmitters. Ingestion of PCP causes prolonged depolarization of the neuron.

Method of absorption

The term "embalming fluid" is often used to refer to the liquid PCP which a cigarette or joint is dipped in, to be ingested through smoking. Smoking PCP is known as "getting wet." There is much confusion over the practice of dipping cigarettes in "embalming fluid" leading some to think that real embalming fluid may actually be used. This is a misconception that may cause serious health consequences beyond those of consuming PCP.

In its powder form, PCP can be insufflated (snorted).

In its pure form, PCP is a white crystalline powder that readily dissolves in water. However, most PCP on the illicit market contains a number of contaminants as a result of makeshift manufacturing, causing the color to range from tan to brown, and the consistency to range from powder to a gummy mass.

Effects

Whether PCP has any strong and consistent effects which are markedly different from other similar compounds is controversial. Some think that the drug's effects are as varied as its appearance. It may be that a moderate amount of PCP will cause users to feel detached, distant, and estranged from their surroundings. Numbness, slurred speech, and loss of coordination may be accompanied by a sense of strength and invulnerability. A blank stare, rapid and involuntary eye movements, diarrhea, and an exaggerated gait are alleged to be among the more observable effects. PCP can sometimes elevate body temperature, which is why many people under the influence of PCP have been known to shed clothing in public places. Acts of violence have been committed by people high on the drug; a well-known example is Brenda Ann Spencer, who claimed to have committed her school massacre while under the influence of alcohol and PCP.

According to the National Institute on Drug Abuse: at high doses of PCP, blood pressure, pulse rate, and respiration drop. This may be accompanied by nausea, vomiting, blurred vision, nystagmus, drooling, loss of balance, and dizziness. High doses of PCP can also cause seizures, coma, and death (though death more often results from accidental injury or suicide during PCP intoxication). High doses can cause symptoms that mimic schizophrenia, such as delusions, hallucinations, paranoia, disordered thinking, a sensation of distance from one's environment, and catatonia. Speech is often sparse and garbled.

References in Popular Culture

- More so than any other illegal substance, PCP has developed an elaborate mythological history surrounding itself, spread by sources such as

D.A.R.E. PCP is said in an urban legend to cause intensely realistic hallucinations, e.g. of spiders engulfing the user's face, causing the user to injure himself in an attempt to remove them. In reality such effects are more like those of a deliriant.

- Among police and firefighters, PCP is treated as a menace. Individuals on PCP are treated almost as bogey-men in personal safety lectures that are loaded with stories involving people on PCP chasing down cars and breaking through walls because they are unable to feel pain.
- One of the street thugs in the Charles Bronson film Death Wish II was portrayed as a PCP user - the scene where he assaults several police officers is reminiscent of an NFL wide receiver evading linemen.
- Another famous mention is in the movie Terminator, where the violent attacks by the character played by Arnold Schwarzenegger, including punching through a windshield without feeling it, are attributed to PCP by the police.
- In an NCIS episode, a supermodel was found dead with PCP in her system.
- In 1981's "Angel Dusted", and again in 1982's "Desperate Lives", characters played by actress Helen Hunt tangle with PCP. After taking PCP in "Angel Dusted", she jumps out a closed second-story window and then gets up and starts scraping her arm violently with a shard of glass.
- American Musician Antron Singleton committed murder and cannibalism while under the effects of PCP.
- On Chappelle's Show, Dave Chappelle is offered PCP by Wayne Brady, which Dave refuses until he is threatened by Wayne (this being a parallel to the movie Training Day.) PCP references abound in the series (perhaps because of Chappelle's upbringing in Washington, D.C., which as mentioned above, is one of the few PCP epicenters in the US)--The World Series of Dice is played by a diceman, Grits n' Gravy, who spends all his winnings on PCP. In the same sketch, one of the characters is named "Ashy Larry," which is slang for PCP. The "angel" in the sketch "It's A Wonderful Chest" attributes his powers to PCP. Also, the character Tyrone Biggums, in his first appearance on the show when he visits a classroom full of schoolchildren to tell them of the dangers of drug use, mentions that he has smoked marijuana laced with "embalming fluid" (see above).
- In the 1995 film "Friday", Chris Tucker's character Smokey mistakenly smokes PCP and develops a twitch that he carries throughout the movie.
- Faith No More has an album titled Angel Dust. It was released in 1992.
- Butthole Surfers released the Live PCPEP in 1984.
- The popular Jackass cast member "Steve-O" documented his 5-day 'trip' on PCP on his DVD "PCP Saved my Life". He precedes the showing of the tape with an announcement, saying he will never watch the tape of his 'trip', and that he will never take PCP again, he remembers no part of the 5-day trip in which he frequently proclaims that PCP has saved his life.
- In Thomas Harris' novel Hannibal, it is described that one of Hannibal Lecter's victims, Mason Verger, performed self-mutilation whilst under the influence of phencyclidine and other drugs that Lecter drugged him with.

- In the second season of the television show Buffy the Vampire Slayer, in the episode School Hard, the principal of the high school covers up a vampire attack by claiming that the attackers were "gang members on PCP."
- In the first manga episodes of City Hunter, Ryo Saeba confronts a syndicated crime group called Union Theope, which uses phencyclidine on some of its agents in order to make them more invulnerable.
- In the 1983 movie Trading Places, Dan Aykroyd is framed for selling PCP.
- 'The Simpsons' featured an episode in which Marge is incorrectly drug-tested positive for "crack and PCP".
- Tupac Shakur mentions PCP in his song "I Ain't Mad at Ya" - "...standin' on the block, wit ya glock, trippin' off sherm..." He also mentioned it in "Hit 'Em Up" - "Smokin' dope, it's like a sherm high/niggas think they learned to fly" and Me & My Girlfriend -"Smokin' sherm drinking malt liquor/father forgive her" (As noted above, "sherm" is a slang name for PCP.)
- Notorious BIG refers to PCP in his song Notorious Thugs and its remix Spit Your Game- "Ain't too many can bang with us/straight up weed no angel dust". He also refers to it in 'Gimme the Loot' - Crazier than a bag of fucking angel dust.
- In Jonathan Caouette's film "Tarnation", he is said to have smoked a PCP-laced joint as a teenager.
- In the System of a Down song "Stealing Society" from the album Hypnotize there is a lyric "crack pipes, needles, PCP and fast cars, kinda mix really well with a dead movie star."
- In the Beastie Boys song "3 Minute Rule" from the album Paul's Boutique there are lyrics by Adrock in which he says, "so peace out y'all, I'm PCP, so I'm out, full throttle to the bottle and full full clout, and I'm out." The Beastie Boys often refer to being 'dusted' in their lyrics, slang for being high on PCP.
- PCP was seen on the television show COPS when a bleeding, naked man punched a hole in a fence and was tackled by many police officers.
- The punk band NOFX released a song on the "Fuck the Kids" album - Eric Melvin VS PCP. Eric Melvin being the bands guitarist.
- The British pop band Right Said Fred released a song named "Angel Dust" on their 2001 album "Fredhead", in which a woman is compared to the effects of the drug.
- In episode 49, the third episode of the third season, of CSI a high school student kills and eats parts of another girl while under the effects of PCP.
- Ghostface Killah often references PCP in his songs such as in Who Are We "...see me in New Orleans, start puffin' on 'sherm" in Apollo Kids "...two culture-ciphers, one bag of wet", the song Ghostface "...now Daddy's blowin' sherm and Remi".
- The British Rock/Electronic band New Order had a track called "Angel Dust" on their Brotherhood album.

- Mitch Hedberg used a joke in which he elaborated on a physical he was required to take to perform on Comedy Central Presents. "To do this show I had to take a physical. They asked me a bunch of medical questions, and they were like, yes or no questions, but they were very strangely worded. Like 'Have you ever tried sugar... or PCP?"
- Calling themselves the "Leak Bros.", rappers Tame One and Cage released an album entitled Waterworld in 2005 on Eastern Conference Records. The entire album was devoted to PCP. "Leak" or "Leaky Leak" is slang for PCP laced marijuana.
- In the popular urban movie Training Day, Ethan Hawke's character smokes marijuana laced with PCP and goes into a stupor-like dream state where everything slows down and the environment changes color.
- Welsh rock band Manic Street Preachers have a song called P.C.P., released as part of a double A-side single, and on their album The Holy Bible. The British metal band Venom released a song named "Angel Dust"
- The PCP in a game called XEvil actually does cause temporary invulnerability and increased strength. However, abusing the drug causes death by overdose. There is a German power metal band named Angel Dust.

See also

- Dissociatives
  - Ketamine
  - Nitrous oxide
  - Dextromethorphan
- Psychoactive drug

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Anti-diabetic drugs

An *anti-diabetic drug* or *oral hypoglycemic agent* is used to treat diabetes mellitus. They usually work by lowering the glucose levels in the blood. There are different types of anti-diabetic drugs, and their use depends on the nature of the diabetes, age and situation of the person, as well as other factors.

Insulin, exenatide, and pramlintide are the only non-oral antidiabetic drugs. Insulin is the mainstay of treatment in Type I diabetes, in which insulin production is impaired. In Type II diabetes, Insulin is used when oral medication has become ineffective. Exenatide and pramlintide are new injectable medications approved in 2005 in the US by the FDA to treat Diabetes mellitus type 2.

Diabetes mellitus

Types of Diabetes

Diabetes mellitus type 1

Diabetes mellitus type 2

Gestational diabetes

Pre-diabetes:
Impaired fasting glycaemia
Impaired glucose tolerance

Disease Management

Diabetes management:

•Diabetic diet

•**Anti-diabetic drugs**

•Conventional insulinotherapy

•Intensive insulinotherapy

Blood tests

Fructosamine

Glucose tolerance test

Glycosylated hemoglobin

Sulfonylureas

Sulfonylureas were the first widely used oral hypoglycemic medications. They are insulin secretagogues, triggering insulin release by direct action on the K***ATP*** channel of the pancreatic beta cells. Eight types of these pills have been marketed in North America, but not all remain available. The "second-generation" drugs are now more commonly used. They are more effective than first-generation drugs and have fewer side effects.

Sulfonylureas bind strongly to plasma proteins. Sulfonylureas are only useful in Type II diabetes, as they work by stimulating endogenous release of insulin. They work best with patients over 40 years old, who have had diabetes mellitus for under ten years. They can not be used with type I diabetes, or diabetes of pregnancy. They can be safely used with metformin or -glitazones. The primary side effect is hypoglycemia.

- First-generation agents
  - tolbutamide (Orinase)

acetohexamide (Dymelor)
tolazamide (Tolinase)
chlorpropamide (Diabinese)

- Second-generation agents
  - glipizide (Glucotrol)

glyburide (Diabeta, Micronase, Glynase)
glimepiride (Amaryl)
gliclazide (Diamicron)

Meglitinides

Meglitinides are related to sulfonylureas and of often called "short-acting secretagogues." The amplification of insulin release is shorter and more intense, and they are taken with meals to boost the insulin response to each meal.

- repaglinide (Prandin) - The max dosage is 16mg/day. Take this drug 0 to 30 minutes prior before eating a meal. If a meal is skipped, then the medication should also be skipped.
- nateglinide (Starlix) - The max dosage is 360 mg/day, usually 120 mg three times a day (TID). It also follows the same recommendations as repaglinide.

Adverse reactions include weight gain and hypoglycemia.

Biguanides

Biguanides reduce hepatic glucose output and increase uptake of glucose by the periphery, including skeletal muscle. Although it must be used with caution in patients with impaired liver or kidney function, metformin has become the most commonly used agent for type 2 diabetes in children and teenagers.

- metformin (Glucophage)
- Phenformin (DBI): used in 1960-1980s, withdrawn due to lactic acidosis risk.

Metformin should be temporarily discontinued before any radiographic procedure involving intravenous iodinated contrast as patients are at an increased risk of lactic acidosis.

Thiazolidinediones

Thiazolidinediones, also known as "glitazones," bind to PPAR[3], a type of nuclear regulatory protein involved in transcription of numerous genes regulating glucose and fat metabolism. They act as "insulin sensitizers" without increasing insulin secretion.

- rosiglitazone (Avandia)

pioglitazone (Actos)
troglitazone (Rezulin): used in 1990s, withdrawn due to hepatitis and liver damage risk.

Alpha glucosidase inhibitors

Alpha glucosidase inhibitors are "diabetes pills" but not technically hypoglycemic agents because they do not have a direct effect on insulin secretion or sensitivity. These agents slow the digestion of starch in the small intestine, so that glucose from the starch of a meal enters the bloodstream more slowly, and can be matched more effectively by an impaired insulin response or sensitivity. These agents are effective by themselves only in the earliest stages of impaired glucose tolerance, but can be helpful in combination with other agents in type 2 diabetes.

- miglitol (Glyset)
acarbose (Precose/Glucobay)

These medications are rarely used in the United States because of the severity of their side effects (flatulence and bloating). They are more commonly prescribed in Europe.

Incretin mimetic

Exenatide (also Exendin-4, marketed as Byetta) is the first of a new class of medications approved for the treatment of type 2 diabetes. It is to be used in conjunction with oral medications such as metformin and/or a sulfonylurea to improve glucose control. The medication is injected twice per day using a specially designed pen. The typical human response is both an improvement of the release of internal insulin by the pancreas and suppression of pancreas glucagon release, behaviors more typical of individuals without blood sugar control problems. In the presence of exenatide, these responses are greater when the blood sugar is elevated.

DPP-4 inhibitors

- Dipeptidyl peptidase-4 (DPP-4) inhibitors (vildagliptin, sitagliptin) increase blood concentration of GLP-1 (glucagon-like peptide-1).

Amylin analogue

- Pramlintide.

Experimental agents

Many other potential drugs are currently in investigation by pharmaceutical companies. Some of these are simply newer members of one of the above classes, but some work by novel mechanisms. For example, at least one compound that enhances the sensitivity of glucokinase to rising glucose is in the stage of animal research. Others are undergoing phase I/II studies.

- PPAR±/³ ligands (muraglitazar and tesaglitazar) - development stopped due to adverse risk profile
- SGLT (sodium-dependent glucose transporter 1) inhibitors increase urinary glucose.
- FBPase (fructose 1,6-bisphosphatase) inhibitors decrease gluconeogenesis in liver.

Insulin by mouth

The basic appeal of oral hypoglycemic agents is that most people would prefer a pill to an injection. Unlike all the oral drugs described in this article, insulin is a protein. Protein hormones, like meat proteins, are digested in the stomach and gut. One alternative delivery

method is by inhalation. In 2006 the U.S. Food and Drug Administration approved the use of Exubera, the first inhalable insulin.

However, the potential market for an oral form of insulin is enormous and many laboratories have attempted to devise ways of moving enough intact insulin from the gut to the portal vein to have a measurable effect on blood sugar. One can find several research reports over the years describing promising approaches or limited success in animals, and limited human testing, but as of 2004, no products appear to be successful enough to bring to market.

Herbal extracts

The first registred use of anti-diabetic drugs was as herbal extracts used by indians in the Amazon Basin for the treatment of type 2 diabetes, and today promoted as vegetable insulin although not formally an insulin analog.[1] The major recent development was done in Brazil around Myrcia sphaerocarpa and other Myrcia species.

"Many countries, especially in the developing world, have a long history of the use of herbal remedies in diabetes (...) STZ diabetic rats were also used to test Myrcia Uniflora extracts (...) "[2].

The usual treatment is with concentrated (root) Myrcia extracts, commercialized in a 4 US dollar per kilogram packed rocks (~100 times cheaper than equivalent artificial drugs), named "Pedra hume de kaá". Phytochemical analysis of the Myrcia extracts reported kinds of flavanone glucosides (myrciacitrins) and acetophenone glucosides (myrciaphenones), and inhibitory activities on aldose reductase and alpha-glucosidase.[3]

A recent review article presents the profiles of plants with hypoglycaemic properties, reported in the literature from 1990 to 2000 and states that "Medical plants play an important role in the management of diabetes mellitus especially in developing countries where resources are meager."[4]

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Diabetes mellitus

ICD-10

E10. — **E**14.

ICD-9

250

MedlinePlus

001214

eMedicine

med/546 emerg/134

MeSH

C18.452.394.750

Diabetes mellitus is a disorder of metabolism, most prominently carbohydrate metabolism. It is a disease characterized by persistent hyperglycemia (high glucose blood sugar). It is a metabolic disease that requires medical diagnosis, treatment and lifestyle changes. The World Health Organization recognizes three main forms of diabetes: type 1, type 2 and gestational diabetes (or type 3, occurring during pregnancy)[1], although these three "types" of diabetes are more accurately considered patterns of pancreatic failure rather than single diseases. Type 1 is generally due to autoimmune destruction of the insulin-producing cells, while type 2 and gestational diabetes are due to insulin resistance by tissues. Type 2 may progress to destruction of the insulin-producing cells of the pancreas, but is still considered Type 2, even though insulin administration may be required.

Since the first therapeutic use of insulin (1921) diabetes has been a treatable but chronic condition, and the main risks to health are its characteristic long-term complications. These include cardiovascular disease (doubled risk), chronic renal failure (it is the main cause for dialysis in developed world adults), retinal damage which can lead to blindness and is the most significant cause of adult blindness in the non-elderly in the developed world, nerve damage, erectile dysfunction (impotence) and gangrene with risk of amputation of toes, feet, and even legs.

Diabetes mellitus

Types of Diabetes

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Diabetes mellitus type 2

Gestational diabetes

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Impaired glucose tolerance

Disease Management

•Anti-diabetic drugs

Blood tests

Fructosamine

Glucose tolerance test

Glycosylated hemoglobin

Terminology

The term diabetes (Greek: ´¹±²®Ä·Â) was coined by Aretaeus of Cappadocia. It is derived from the Greek ´¹±²±¯½µ¹½, diabaínein that literally means "passing through," or "siphon," a reference to one of diabetes' major symptoms—excessive urine production. In 1675 Thomas Willis added mellitus from the Latin word for honey (mel in the sense of "honey sweet") when he noted that the blood and urine of a diabetic has a sweet taste. This had been noticed long before in ancient times by the Greeks, Chinese, Egyptians, and Indians. In 1776 Matthew Dobson confirmed the sweet taste was because of an excess of a kind of sugar in the urine and blood of people with diabetes.[2]

The ancient Indians tested for diabetes by observing whether ants were attracted to a person's urine, and called the ailment "sweet urine disease" (Madhumehalai); medieval European doctors tested for it by tasting the urine themselves, a scene which was occasionally depicted in Gothic reliefs.

While the term diabetes without a modifier usually refers to diabetes mellitus, there is another, rarer condition named diabetes insipidus (unquenchable diabetes) in which the urine is not sweet; it can be caused by either kidney (nephrogenic DI) or pituitary gland (central DI) damage.

History

Although diabetes has been recognized since antiquity, and treatments of various efficacy have been known in various regions since the Middle Ages, and in legend for much longer, the elucidation of the pathogenesis of diabetes occurred mainly in the 20th century.[3] The discovery of the role of the pancreas in diabetes is generally ascribed to Joseph von Mering and Oskar Minkowski, European researchers who in 1889 found that when they completely removed the pancreas of dogs, the dogs developed all the signs and symptoms of diabetes and died shortly afterward.[4] In 1910, Sir Edward Albert Sharpey-Schafer of Edinburgh suggested that people with diabetes were deficient in a single chemical that was normally produced by the pancreas—he proposed calling this substance insulin. The term is derived from the Latin insula, meaning island, in reference to the islets of Langerhans in the pancreas that produce insulin.[3]

The endocrine role of the pancreas in metabolism, and indeed the existence of insulin, was not fully clarified until 1921, when Sir Frederick Grant Banting and Charles Herbert Best repeated the work of Von Mering and Minkowski, but went further and demonstrated that they could reverse induced diabetes in dogs by giving them an extract from the pancreatic islets of Langerhans of healthy dogs.[5] Banting, Best, and colleagues (particularly the chemist Collip) went on to isolate the hormone insulin from bovine pancreases at the University of Toronto in Canada. This led to the availability of an effective treatment—insulin injections—and the first clinical patient was treated in 1922. For this, Banting and MacLeod received the Nobel Prize in Physiology or Medicine in 1923; both shared their Prize money with others in the team who were not recognized, in particular Best and Collip. Banting and Best made the patent available without charge and did not attempt to control commercial production. Insulin production and therapy rapidly spread around the world, largely as a result of this decision.

Despite the availability of treatment, diabetes remained a major cause of death. For instance, statistics reveal that the cause-specific mortality rate during 1927 amounted to about 47.7 per 100,000 population in Malta.[6]

The distinction between what is now known as type 1 diabetes and type 2 diabetes was first clearly made by Sir Harold Percival (Harry) Himsworth in 1935 and was published in January 1936.[7]

Other landmark discoveries include:[3]

- identification of the first of the sulfonylureas in 1942
the radioimmunoassay for insulin, as discovered by Rosalyn Yalow and Solomon Berson (gaining Yalow the 1977 Nobel Prize in Physiology or Medicine)[8]

Dr Gerald Reaven's identification of the constellation of symptoms now called metabolic syndrome in 1988
Demonstration that intensive glycemic control in type 1 diabetes reduces chronic side effects more as glucose levels approach 'normal' in a large longitudinal study[9], and also in type 2 diabetics in other large studies
identification of the first thiazolidinedione as an effective insulin sensitizer during the 1990's
Self monitoring of glucose in the home via a finger-stick blood sample and a battery powered meter in the 1970's.[10]

Causes & types

Glucose metabolism

Since insulin is the principal hormone that regulates uptake of glucose into most cells from the blood (primarily muscle and fat cells, but not central nervous system cells), deficiency of insulin or the insensitivity of its receptors plays a central role in all forms of diabetes mellitus.

Much of the carbohydrate in food is converted within a few hours to the monosaccharide glucose, the principal carbohydrate in blood. Some carbohydrates are not; fruit sugar (fructose) is usable as cellular fuel but is not converted to glucose and does not participate in the insulin / glucose metabolic regulatory mechanism, nor does the carbohydrate cellulose (though it is actually many glucoses in long chains) as humans and many animals have no digestive pathway capable of handling it. Insulin is released into the blood by beta cells (^{2}-cells) in the pancreas in response to rising levels of blood glucose (e.g., after a meal). Insulin enables most body cells (about 2/3 is the usual estimate, including muscle cells and adipose tissue) to absorb glucose from the blood for use as fuel, for conversion to other needed molecules, or for storage. Insulin is also the principal control signal for conversion of glucose (the basic sugar used for fuel) to glycogen for internal storage in liver and muscle cells. Reduced insulin levels result both in the reduced release of insulin from the beta cells and in the reverse conversion of glycogen to glucose when glucose levels fall, although only glucose thus recovered by the liver re-enters the bloodstream as muscle cells lack the necessary export mechanism.

Higher insulin levels increase many anabolic ("building up") processes such as cell growth and duplication, protein synthesis, and fat storage. Insulin is the principal signal in converting many of the bidirectional processes of metabolism from a catabolic to an anabolic direction, and vice versa. In particular, it is the trigger for entering or leaving ketosis (ie, the fat burning metabolic phase).

If the amount of insulin available is insufficient, if cells respond poorly to the effects of insulin (insulin insensitivity or resistance), or if the insulin itself is defective, glucose will not be handled properly by body cells (about T require it) or stored appropriately in the liver and muscles. The net effect is persistent high levels of blood glucose, poor protein synthesis, and other metabolic derangements, such as acidosis.

Type 1 diabetes mellitus

Type 1 diabetes mellitus - formerly known as insulin-dependent diabetes (IDDM), childhood diabetes, or juvenile-onset diabetes - is characterized by loss of the insulin-producing beta cells of the islets of Langerhans of the pancreas leading to a deficiency of insulin. Sensitivity and responsiveness to insulin are usually normal, especially in the early stages. This type comprises up to 10% of total cases in North America and Europe, though this varies by geographical location. This type of diabetes can affect children or adults, but has traditionally been termed "juvenile diabetes" because it represents a majority of cases of diabetes affecting children. The most common cause of beta cell loss leading to type 1 diabetes is autoimmune destruction, accompanied by antibodies directed against insulin and islet cell proteins. The principal treatment of type 1 diabetes, even from the earliest stages, is replacement of insulin. Without insulin, ketosis and diabetic ketoacidosis can develop and coma or death will result.

Currently, type 1 diabetes can be treated only with insulin, with careful monitoring of blood glucose levels using blood testing monitors. Emphasis is also placed on lifestyle adjustments (diet and exercise). Apart from the common subcutaneous injections, it is also possible to deliver insulin via a pump, which allows infusion of insulin 24 hours a day at preset levels, and the ability to program a push dose (a bolus) of insulin as needed at meal times. This is at the expense of an indwelling subcutaneous catheter. It is also possible to deliver insulin via an inhaled powder.

Type 1 treatment must be continued indefinitely at present. Treatment does not impair normal activities, if sufficient awareness, appropriate care, and discipline in testing and medication. The average glucose level for the type 1 patient should be as close to normal (80–120 mg/dl, 4–6 mmol/l) as possible. Some physicians suggest up to 140–150 mg/dl (7-7.5 mmol/l) for those having trouble with lower values, such as frequent hypoglycemic events. Values above 200 mg/dl (10 mmol/l) are often accompanied by discomfort and frequent urination leading to dehydration. Values above 300 mg/dl (15 mmol/l) usually require immediate treatment and may lead to ketoacidosis. Low levels of blood glucose, called hypoglycemia, may lead to seizures or episodes of unconsciousness.

Type 2 diabetes mellitus

Type 2 diabetes mellitus - previously known as adult-onset diabetes, maturity-onset diabetes, or non-insulin dependent diabetes mellitus (NIDDM) - is due to a combination of defective insulin secretion and defective responsiveness to insulin (often termed insulin resistance or reduced insulin sensitivity), almost certainly involving the insulin receptor in cell membranes. In early stages, the predominant abnormality is reduced insulin sensitivity, characterized by elevated levels of insulin in the blood. In the early stages, hyperglycemia can be reversed by a variety of measures and medications that improve insulin sensitivity or reduce glucose production by the liver, but as the disease progresses the impairment of insulin secretion worsens, and therapeutic replacement of insulin often becomes necessary. There are numerous theories as to the exact cause and mechanism for this resistance, but central obesity (fat concentrated around the waist in relation to abdominal organs, not it

seems, subcutaneous fat) is known to predispose for insulin resistance, possibly due to its secretion of adipokines (a group of hormones) that impair glucose tolerance. Abdominal fat is especially active hormonally. Obesity is found in approximately 90% of Developed world patients diagnosed with type 2 diabetes. Other factors may include aging and family history, although in the last decade it has increasingly begun to affect children and adolescents.

Type 2 diabetes may go unnoticed for years in a patient before diagnosis, since the symptoms are typically milder (e.g. lack of ketoacidotic episodes) and can be sporadic. However, severe complications can result from unnoticed type 2 diabetes, including renal failure, vascular disease (including coronary artery disease), vision damage, etc.

Type 2 diabetes is usually first treated by changes in physical activity (usually increase), diet (generally decrease carbohydrate intake, especially glucose generating carbohydrates), and through weight loss. These can restore insulin sensitivity, even when the weight loss is modest, for example, around 5 kg (10 to 15 lb), most especially when it is in abdominal fat deposits. The next step, if necessary, is treatment with oral antidiabetic drugs. As insulin production is initially unimpaired, oral medication (often used in combination) can still be used that improves insulin production (eg, sulfonylureas) and regulate inappropriate release of glucose by the liver (and attenuate insulin resistance to some extent (eg, metformin), and substantially attenuate insulin resistance (eg, thiazolidinediones). If these fail, insulin therapy will be necessary to maintain normal or near normal glucose levels. A disciplined regimen of blood glucose checks is recommended in most cases, most particularly and necessarily when taking most of these medications.

Gestational diabetes

Gestational diabetes, Type 3, also involves a combination of inadequate insulin secretion and responsiveness, resembling type 2 diabetes in several respects. It develops during pregnancy and may improve or disappear after delivery. Even though it may be transient, gestational diabetes may damage the health of the fetus or mother, and about 20%–50% of women with gestational diabetes develop type 2 diabetes later in life.

Gestational diabetes mellitus occurs in about 2%–5% of all pregnancies. It is temporary, and fully treatable, but, if untreated, may cause problems with the pregnancy, including macrosomia (high birth weight) of the child. It requires careful medical supervision during the pregnancy.

Other types

There are several rare causes of diabetes mellitus that do not fit into type 1, type 2, or gestational diabetes:

- Genetic defects in beta cells (autosomal or mitochondrial)
- Genetically-related insulin resistance, with or without lipodystrophy (abnormal body fat deposition)
- Diseases of the pancreas (e.g. chronic pancreatitis, cystic fibrosis)
- Hormonal defects
- Chemicals or drugs

The tenth version of the International Statistical Classification of Diseases (ICD-10) contained a diagnostic entity named "malnutrition-related diabetes mellitus" (MRDM or MMDM, ICD-10 code E12). A subsequent WHO 1999 working group recommended that MRDM be deprecated, and proposed a new taxonomy for alternative forms of diabetes.[1] Classifications of non-type 1, non-type 2, non-gestational diabetes remains controversial.

Genetics

Both type 1 and type 2 diabetes are at least partly inherited. Type 1 diabetes appears to be triggered by some (mainly viral) infections, or in a less common group, by stress or environmental factors (such as exposure to certain chemicals or drugs). There is a genetic element in individual susceptibility to some of these triggers which has been traced to particular HLA genotypes (i.e. genetic "self" identifiers used by the immune system). However, even in those who have inherited the susceptibility, type 1 diabetes mellitus seems to require an environmental trigger. A small proportion of people with type 1 diabetes carry a mutated gene that causes maturity onset diabetes of the young (MODY).

There is a rather stronger inheritance pattern for type 2 diabetes. Those with first-degree relatives with type 2 have a much higher risk of developing type 2. Concordance among monozygotic twins is close to 100% , and 25% of those with the disease have a family history of diabetes. It is also often connected to obesity, which is found in approximately 85% of (North American) patients diagnosed with this type, so some experts believe that inheriting a tendency toward obesity also contributes.

Diagnosis

Signs and symptoms

The classical triad of diabetes symptoms is polyuria (frequent urination), polydipsia (increased thirst, and consequent increased fluid intake) and polyphagia (increased appetite). These symptoms may develop quite fast in type 1, particularly in children (weeks or months), but may be subtle or completely absent - as well as developing much more slowly - in type 2. In type 1 there may also be weight loss (despite normal or increased eating), increased appetite, and irreducible fatigue. These symptoms may also manifest in type 2 diabetes in patients whose diabetes is poorly controlled.

Thirst develops because of osmotic effects—sufficiently high glucose (above the "renal threshold") in the blood is excreted by the kidneys, but this requires water to carry it and causes increased fluid loss, which must be replaced. The lost blood volume will be replaced from water held inside body cells, causing dehydration. Prolonged high blood glucose causes changes in the shape of the lens in the eye, leading to vision changes. Blurred vision is a common complaint leading to a diagnosis of type 1; it should always be suspected in such cases.

Patients (usually with type 1 diabetes) may also present with diabetic ketoacidosis (DKA), an extreme state of dysregulation characterized by the smell of acetone on the patient's breath, Kussmaul breathing (a rapid, deep breathing), polyuria, nausea, vomiting

and abdominal pain and any of many altered state of consciousness or arousal (eg, hostility and mania or, equally, confusion and lethargy). In severe DKA, coma (unconsciousness) may follow, progressing to death if untreated. In any form, DKA is a medical emergency and requires expert attention.

A rarer but equally severe presentation is hyperosmolar nonketotic state, which is more common in type 2 diabetes, and is mainly the result of dehydration due to the polyuria. Often, the patient has been drinking extreme amounts of sugar-containing drinks, leading to a vicious circle in regard to water loss.

Diagnostic approach

The diagnosis of type 1 diabetes and many cases of type 2 is usually prompted by recent-onset symptoms of excessive urination (polyuria) and excessive thirst (polydipsia), often accompanied by weight loss. These symptoms typically worsen over days to weeks; about 25% of people with new type 1 diabetes have developed a degree of diabetic ketoacidosis by the time the diabetes is recognized. The diagnosis of other types of diabetes is usually made in many other ways. The most common are (1) health screening, (2) detection of hyperglycemia when a doctor is investigating a complication of longstanding, unrecognized diabetes, and (3) new signs and symptoms attributable to the diabetes.

1. Diabetes screening is recommended for many types of people at various stages of life or with several different risk factors. The screening test varies according to circumstances and local policy and may be a random glucose, a fasting glucose and insulin, a glucose two hours after 75 g of glucose, or a formal glucose tolerance test. Many healthcare providers recommend universal screening for adults at age 40 or 50, and sometimes occasionally thereafter. Earlier screening is recommended for those with risk factors such as obesity, family history of diabetes, high-risk ethnicity (Hispanic/Latin American, American Indian, African American, Pacific Island, and South Asian ancestry).
2. Many medical conditions are associated with a higher risk of various types of diabetes and warrant screening. A partial list includes: high blood pressure,
3. elevated cholesterol levels, coronary artery disease, past gestational diabetes, polycystic ovary syndrome, chronic pancreatitis, fatty liver, hemochromatosis, cystic fibrosis, several mitochondrial neuropathies and myopathies, myotonic dystrophy, Friedreich's ataxia, some of the inherited forms of neonatal hyperinsulinism, and many others. Risk of diabetes is higher with chronic use of several medications, including high-dose glucocorticoids, some chemotherapy agents (especially L-asparaginase), and some of the antipsychotics and mood stabilizers (especially phenothiazines and some atypical antipsychotics).
Diabetes is often detected when a person suffers a problem frequently caused by diabetes, such as a heart attack, stroke, neuropathy, poor wound healing or a foot ulcer, certain eye problems, certain fungal infections, or delivering a baby with macrosomia or hypoglycemia.

Diagnostic criteria

Diabetes mellitus is characterized by recurrent or persistent hyperglycemia, and is diagnosed by demonstrating any one of the following:[1]

- fasting plasma glucose level at or above 126 mg/dL or 7.0 mmol/l.
- plasma glucose at or above 200 mg/dL or 11.1 mmol/l two hours after a 75 g oral glucose load in a glucose tolerance test.
- random plasma glucose at or above 200 mg/dL or 11.1 mmol/l.

A positive result should be confirmed by any of the above-listed methods on a different day, unless there is no doubt as to the presence of significantly-elevated glucose levels. Most physicians prefer measuring a fasting glucose level because of the ease of measurement and time commitment of formal glucose tolerance testing, which can take two hours to complete. By definition, two fasting glucose measurements above 126 mg/dL or 7.0 mmol/l is considered diagnostic for diabetes mellitus.

Patients with fasting sugars between 6.1 and 7.0 mmol/l (110 and 125 mg/dL) are considered to have "impaired fasting glucose" and patients with plasma glucose at or above 140mg/dL or 7.8 mmol/l two hours after a 75 g oral glucose load are considered to have "impaired glucose tolerance". "Prediabetes" is either impaired fasting glucose or impaired glucose tolerance; the latter in particular is a major risk factor for progression to full-blown diabetes mellitus as well as cardiovascular disease.

While not used for diagnosis, an elevated level of glucose bound to hemoglobin (termed glycosylated hemoglobin or HbA1c) of 6.0% or higher (2003 revised U.S. standard) is considered abnormal by most labs; HbA1c is primarily a treatment-tracking test reflecting average blood glucose levels over the preceding 90 days (approximately). However, some physicians may order this test at the time of diagnosis to track changes over time. The current recommended goal for HbA1c in patients with diabetes is <7.0%, as defined as "good glycemic control", although some guidelines are stricter (<6.5%). People with diabetes that have HbA1c levels within this goal have a significantly lower incidence of complications from diabetes, including retinopathy and diabetic nephropathy.[11]

Complications

The complications are far less common and less severe in people who have well-controlled blood sugar levels.[12] [13] In fact, the better the control, the lower the risk of complications. Hence patient education, understanding and participation is vital. Healthcare professionals who treat diabetes also address other health problems that may accelerate the deleterious effects of diabetes. These include smoking (abstain), elevated cholesterol levels (control with diet, exercise or medication), obesity (even modest weight loss can be beneficial), high blood pressure, and lack of regular exercise.

Acute

Diabetic ketoacidosis

Diabetic ketoacidosis (DKA) is an acute, dangerous complication and is always a medical emergency. On presentation at hospital, the patient in DKA is typically dehydrated and breathing both fast and deeply. Abdominal pain is common and may be severe. The level of consciousness is normal until late in the process, when lethargy (dulled or reduced level of alertness or consciousness) may progress to coma. The ketoacidosis can become severe enough to cause hypotension and shock. Prompt proper treatment usually results in full recovery, though death can result from inadequate treatment, delayed treatment or from a variety of complications. It is much more common in type 1 diabetes than type 2, but can still occur in patients with type 2 diabetes.

Nonketotic hyperosmolar coma

While not always progressing to coma, this hyperosmolar nonketotic state (HNS) is another acute problem associated with diabetes mellitus. It has many symptoms in common with DKA, but a different cause, and requires different treatment. In anyone with very high blood glucose levels (usually considered to be above 300 mg/dl or 16 mmol/l), water will be osmotically driven out of cells into the blood. The kidneys will also be "dumping" glucose into the urine, resulting in concomitant loss of water, causing an increase in blood osmolality. If the fluid is not replaced (by mouth or intravenously), the osmotic effect of high glucose levels combined with the loss of water will eventually result in such a high serum osmolality (dehydration). The body's cells may become progressively dehydrated as water is drawn out from them and excreted. Electrolyte imbalances are also common. This combination of changes, especially if prolonged, will result in symptoms of lethargy (dulled or reduced level of alertness or consciousness) and may progress to coma. As with DKA urgent medical treatment is necessary, especially volume replacement. This is the diabetic coma which more commonly occurs in type 2 diabetics.

Hypoglycemia

Hypoglycemia, or abnormally low blood glucose, is a complication of several diabetes treatments. It may develop if the glucose intake does not match the treatment. The patient may become agitated, sweaty, and have many symptoms of sympathetic activation of the autonomic nervous system resulting in feelings similar to dread and immobilized panic. Consciousness can be altered, or even lost, in extreme cases, leading to coma and/or seizures or even brain damage and death. In patients with diabetes this can be caused by several factors, such as too much or incorrectly timed insulin, too much exercise or incorrectly timed exercise (which decreases insulin requirements) or not enough food or insufficient amount of carbohydrates in food. In most cases, hypoglycemia is treated with sweet drinks or food. In severe cases, an injection of glucagon (a hormone with the opposite effects of insulin) or an intravenous infusion of glucose is used for treatment, but usually only if the diabetic is unconscious.

Chronic

Microvascular disease

Chronic elevation of blood glucose level leads to damage of blood vessels. In diabetes, the resultant problems are grouped under "microvascular disease" (due to damage to small blood vessels) and "macrovascular disease" (due to damage to the arteries).

The damage to small blood vessels leads to a microangiopathy, which causes the following organ-related problems:

- Diabetic retinopathy, growth of friable and poor-quality new blood vessels in the retina as well as macular edema (swelling of the macula), which can lead to severe vision loss or blindness. Retinal damage (from microangiopathy) makes it the most common cause of blindness among non-elderly adults in the US.
- Diabetic neuropathy, abnormal and decreased sensation, usually in a stocking distribution starting at the feet but potentially in other nerves. When combined with damaged blood vessels this can lead to diabetic foot (see below). Other forms of diabetic neuropathy may present as mononeuritis or autonomic neuropathy.
- Diabetic nephropathy, damage to the kidney which can lead to chronic renal failure, eventually requiring dialysis. Diabetes mellitus is the most common cause of adult kidney failure worldwide.

Macrovascular disease

Macrovascular disease leads to cardiovascular disease, mainly by accelerating atherosclerosis:

- Coronary artery disease, leading to myocardial infarction ("heart attack") or angina
 Stroke (mainly ischemic type)
 Peripheral vascular disease, which contributes to intermittent claudication (exertion-related foot pain) as well as diabetic foot.
 Diabetic myonecrosis

Diabetic foot, often due to a combination of neuropathy and arterial disease, may cause skin ulcer and infection and, in serious cases, necrosis and gangrene. It is the most common cause of adult amputation, usually of toes and or feet, in the US and other Western countries.

Carotid artery stenosis does not occur more often in diabetes, and there appears to be a lower prevalence of abdominal aortic aneurysm. However, diabetes does cause higher morbidity, mortality and operative risks with these conditions.[14]

Treatment and management

Diabetes is a chronic disease, and emphasis is on managing short-term as well as long-term diabetes-related problems. There is an important role for patient education, nutritional support, self glucose monitoring, as well as long-term glycemic control. A scrupulous control is needed to help reduce the risk of long term complications. In addition, given the associated higher risks of cardiovascular disease, lifestyle modifications must be implemented to

control blood pressure[15] and cholesterol by exercising more, smoking cessation, and consuming an appropriate diet.

In countries with a general practitioner system, such as the United Kingdom, care may be extended mainly in the community, with hospital-based specialist input only in case of complications, difficult blood sugar control, or participation in research. In other circumstances, general practitioners and specialists may share care of a patient in a team approach. Optometrists, podiatrists/chiropodists, dietitians, physiotherapists, clinical nurse specialists (eg, Certified Diabetic Educators), or nurse practitioners may provide multidisciplinary expertise.

Nowadays, with improved diagnostic support, type-1 (insulin-dependent) diabetics can join all kinds of activities. In May 2006 for example, the Austrian mountaineer Geri Winkler became the first insulin-dependent diabetic to reach the top of Mount Everest.

Curing diabetes

The fact that type 1 diabetes is due to the failure of one of the cell types of a single organ with a relatively simple function (i.e. the failure of the islets of Langerhans) has led to the study of several possible schemes to cure diabetes.[16] In contrast, type 2 diabetes is more complex with fewer prospects of a curative measure, but further understanding of the underlying mechanism of insulin resistance may make a cure possible. Correcting insulin resistance may provide a cure for type 2 diabetes.[17]

Only those type 1 diabetics who have received a kidney-pancreas transplant (when they have developed diabetic nephropathy) and become insulin-independent may be considered "cured" from their diabetes. Still, they generally remain on long-term immunosuppressive drug and there is a possibility the autoimmune phenomenon will develop in the transplanted organ.[16]

Transplants of exogenous beta cells have been performed experimentally in both mice and humans, but this measure is not yet practical in regular clinical practice. Thus far, like any such transplant, it provokes an immune reaction and long-term immunosuppressive drug will be needed to protect the transplanted tissue.[18] An alternative technique has been proposed to place the transplanted beta cells in a semi-permeable container, isolating them from the immune system. Stem cell research has also been suggested as a potential avenue for a cure since it may permit the regrowth of islet cells which are genetically part of the treated individual, thus eliminating the need for immuno-suppressants. However, it has also been hypothesised that the same mechanism which led to islet destruction originally may simply destroy even stem-cell regenerated islets.[16]

Microscopic or nanotechnological approaches are under investigation as well, with implanted stores of insulin metered out by a rapid response valve sensitive to blood glucose levels. At least two approaches have been proposed and demonstrated in vitro. These are, in some sense, closed-loop insulin pumps.

Prevention

As little is known on the exact mechanism by which type 1 diabetes develops, there are no preventive measures available for that form of diabetes. Some studies have attributed a protective effect of breastfeeding on the development of type 1 diabetes.

Type 2 diabetes can be prevented in many cases by making changes in diet and increasing physical activity.[19] Some studies have shown delayed progression to diabetes in predisposed patients through the use of metformin[19] or valsartan.[20] Breastfeeding might also be correlated with the prevention of type 2 of the disease in mothers.[21]

As of late 2006, although there are many claims of nutritional cures, there is no reliable proof of their effectiveness. In addition, despite claims by some that vaccinations may cause diabetes, there are no studies proving any such connection.

Public health and policy

The 1989 Declaration of St Vincent was the result of international efforts to improve the care accorded to those with diabetes. Doing so is important both in terms of quality of life and life expectancy but also economically - expenses to diabetes have been shown to be a major drain on health- and productivity-related resources for healthcare systems and governments.

Several countries established more and less successful national diabetes programmes to improve treatment of the disease.[22]

Epidemiology and statistics

In 2006, according to the World Health Organization, at least 171 million people worldwide suffer from diabetes. Its incidence is increasing rapidly, and it is estimated that by the year 2030, this number will double. Diabetes mellitus occurs throughout the world, but is more common (especially type 2) in the more developed countries. The greatest increase in prevalence is, however, expected to occur in Asia and Africa, where most patients will likely be found by 2030. The increase in incidence of diabetes in developing countries follows the trend of urbanization and lifestyle changes, perhaps most importantly a "Western-style" diet. This has suggested an environmental (i.e., dietary) effect, but there is little understanding of the mechanism(s) at present, though there is much speculation, some of it most compellingly presented.

Diabetes is in the top 10, and perhaps the top 5, of the most significant diseases in the developed world, and is gaining in significance there and elsewhere.

For at least 20 years, diabetes rates in North America have been increasing substantially. In 2005 there are about 20.8 million people with diabetes in the United States alone. According to the American Diabetes Association, there are about 6.2 million people undiagnosed and about 41 million people that would be considered prediabetic.[23] However, the criteria for diagnosing diabetes in the USA means that it is more readily diagnosed than in some other countries. The Centers for Disease Control has termed the change an epidemic. The National Diabetes Information Clearinghouse estimates that

diabetes costs $132 billion in the United States alone every year. About 5%–10% of diabetes cases in North America are type 1, with the rest being type 2. The fraction of type 1 in other parts of the world differs; this is likely due to both differences in the rate of type 1 and differences in the rate of other types, most prominently type 2. Most of this difference is not currently understood.According to the American Diabetes Association, 1 in 3 Americans born after 2000 will develop diabetes in their lifetime.[24]

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Alpha-glucosidase inhibitors

*Alpha-glucosidase inhibitor*s are oral anti-diabetic drugs used for diabetes mellitus type 2 that work by preventing the digestion of complex carbohydrates (such as starch). Complex carbohydrates are normally converted into simple sugars (monosaccharides) which can be absorbed through the intestine. Hence, alpha-glucosidase inhibitors reduce the impact of complex carbohydrates on blood sugar.

Examples and differences

Examples of alpha-glucosidase inhibitors include:

- Acarbose

Miglitol

Even though the drugs have a similar mechanism of action, there are subtle differences between acarbose and miglitol. Acarbose is an oligosaccharide, whereas miglitol resembles a monosaccharide. Miglitol is fairly well-absorbed by the body, as opposed to acarbose. Moreover, acarbose inhibits pancreatic alpha-amylase in addition to alpha-glucosidase.

Role in clinical use

Alpha-glucosidase inhibitors are used to establish greater glycemic control over hyperglycemia in diabetes mellitus type 2, particularly with regard to postprandial hyperglycemia. They may be used as monotherapy in conjunction with an appropriate diabetic diet and exercise, or they may be used in conjunction with other anti-diabetic drugs.

Alpha-glucosidase inhibitors may also be useful in patients with diabetes mellitus type 1; however, this use has not been officially approved by the Food and Drug Administration.

Mechanism of action

Alpha-glucosidase inhibitors are saccharides that act as competitive inhibitors of enzymes needed to digest carbohydrates: specifically alpha-glucosidase enzymes in the brush border of the small intestines. The membrane-bound intestinal alpha-glucosidases hydrolyze oligosaccharides, trisaccharides, and disaccharides to glucose and other monosaccharides in the small intestine.

Acarbose also blocks pancreatic alpha-amylase in addition to inhibiting membrane-bound alpha-glucosidases. Pancreatic alpha-amylase hydrolyzes complex starches to oligosaccharides in the lumen of the small intestine.

Inhibition of these enzyme systems reduces the rate of digestion of complex carbohydrates. Less glucose is absorbed because the carbohydrates are not broken down into glucose molecules. In diabetic patients, the short-term effect of these drugs therapies is to decrease current blood glucose levels: the long term effect is a small reduction in hemoglobin A1c level. (From Drug Therapy in Nursing, 2nd ed)

Dosing

Since alpha-glucosidase inhibitors are competitive inhibitors of the digestive enzymes, they must be taken at the start of main meals to have maximal effect. Their effects on blood sugar levels following meals will depend on the amount of complex carbohydrates in the meal.

Side effects & precautions

Since alpha-glucosidase inhibitors prevent the degradation of complex carbohydrates into glucose, the carbohydrates will remain in the intestine. In the colon, bacteria will digest the complex carbohydrates, thereby causing gastrointestinal side effects such as flatulence

and diarrhea. Since these effects are dose-related, it is generally advised to start with a low dose and gradually increase the dose to the desired amount.

If a patient using an alpha-glucosidase inhibitor suffers from a bout of hypoglycemia, the patient should eat something containing monosaccharides, such as glucose tablets. Since the drug will prevent the digestion of complex carbohydrates, starchy foods may not effectively reverse a hypoglycemic episode in a patient taking an alpha-glucosidase inhibitor.

Dipeptidyl peptidase-4 inhibitors

Dipeptidyl peptidase 4 inhibitors, also *DPP-4 inhibitors*, are a new class of oral hypoglycemics. Their mechanism of action is thought to result from increased GLP-1,[1][2] which inhibits glucagon release (which increases the blood glucose).

Drugs belonging to this class are vildagliptin and sitagliptin.

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Insulin therapies

Insulin crystals

Other names: *insulin*

Genetic data

Locus: Chr. 11 p15.5

Gene code: HUGO code:INS

Gene type: Protein coding

Protein Structure/Function

Molecular Weight: 11982 (Da)

Structure: Solution Structure of Human pro-Insulin Polypeptide

Protein type: insulin family

Functions: glucose regulation

Domains: INS domain

Motifs: SP motif

Other

Taxa expressing: Homo sapiens; homologs: in metazoan taxa from invertebrates to mammals

Cell types: pancreas: beta cells of the Islets of Langerhans

Subcellular localization: extracellular fluids

Covalent modifications: glycation, proteolytic cleavage

Pathway(s): Insulin signaling pathway (KEGG); Type II diabetes mellitus (KEGG); Type I diabetes mellitus (KEGG); Maturity onset diabetes of the young (KEGG); Regulation of actin cytoskeleton (KEGG)

Receptor/Ligand data

Antagonists: glucagon, steroids, most stress hormomes

Medical/Biotechnological data

Diseases: familial hyperproinsulinemia, Diabetes mellitus

Pharmaceuticals: insulin (Humulin Novolin), insulin lispro (Humalog), insulin aspart (Novolog), insulin detemir (Levemir), insulin glargine (Lantus), etc

Insulin (from Latin insula, "island", as it is produced in the Islets of Langerhans in the pancreas) is a polypeptide hormone that regulates carbohydrate metabolism. Apart from being the primary effector in carbohydrate homeostasis, it has effects on fat metabolism and it can change the liver's ability to release fat stores. Insulin's concentration has extremely widespread effects throughout the body.

Insulin is used medically in some forms of diabetes mellitus. Patients with type 1 diabetes mellitus depend on exogenous insulin (commonly injected subcutaneously) for their survival because of an absolute deficiency of the hormone; patients with type 2 diabetes mellitus have either relatively low insulin production or insulin resistance or both, and a non-trivial fraction of type 2 diabetics eventually require insulin administration when other medications become inadequate in controlling blood glucose levels.

Insulin has a molecular weight of 5808 Da. It has the molecular formula $C_{257}H_{383}N_{65}O_{77}S_{6}$.

Insulin structure varies slightly between species of animal. Its carbohydrate metabolism regulatory function strength in humans also varies. Porcine (pig) insulin is particularly close to humans'.

Discovery and characterization

In 1869 Paul Langerhans, a medical student in Berlin, was studying the structure of the pancreas under a microscope when he noticed some previously-unidentified cells scattered in the exocrine tissue. The function of the "little heaps of cells," later known as the Islets of Langerhans, was unknown, but Edouard Laguesse later argued that they may produce a secretion that plays a regulatory role in digestion.

In 1889, the Polish-German physician Oscar Minkowski in collaboration with Joseph von Mehring removed the pancreas from a healthy dog to demonstrate this assumed role in digestion. Several days after the dog's pancreas was removed, Minkowski's animal keeper noticed a swarm of flies feeding on the dog's urine. On testing the urine they found that there was sugar in the dog's urine, demonstrating for the first time the relationship between the pancreas and diabetes. In 1901, another major step was taken by Eugene Opie, when he clearly established the link between the Islets of Langerhans and diabetes: Diabetes mellitus.... is caused by destruction of the islets of Langerhans and occurs only when these bodies are in part or wholly destroyed. Before this demonstration, the link between the pancreas and diabetes was clear, but not the specific role of the islets.

Over the next two decades, several attempts were made to isolate the secretion of the islets as a potential treatment. In 1906 George Ludwig Zuelzer was partially successful treating dogs with pancreatic extract, but was unable to continue his work. Between 1911 and 1912, E.L. Scott at the University of Chicago used aqueous pancreatic extracts and noted a slight diminution of glycosuria, but was unable to convince his director and the research was shut down. Israel Kleiner demonstrated similar effects at Rockefeller University in 1919, but his work was interrupted by World War I and he was unable to return to it. Nicolae Paulescu, a professor of physiology at the Romanian School of Medicine, published similar work in 1921 that was carried out in France and patented in Romania, and it has been argued ever since that he is the rightful discoverer.

However, the Nobel prizes committee in 1923 credited the practical extraction of insulin to a team at the University of Toronto. In October 1920, Frederick Banting was reading one of Minkowski's papers and concluded that it is the very digestive secretions that Minkowski had originally studied that were breaking down the secretion, thereby making it impossible to extract successfully. He jotted a note to himself Ligate pancreatic ducts of the dog. Keep dogs alive till acini degenerate leaving islets. Try to isolate internal secretion of these and relieve glycosurea.

He travelled to Toronto to meet with J.J.R. Macleod, who was not entirely impressed with his idea. Nevertheless, he supplied Banting with a lab at the University, an assistant, medical student Charles Best, and ten dogs, while he left on vacation during the summer of 1921. Their method was tying a ligature (string) around the pancreatic duct, and, when examined several weeks later, the pancreatic digestive cells had died and been absorbed by the immune system, leaving thousands of islets. They then isolated the protein from these islets to produce what they called isletin. Banting and Best were then able to keep a pancreatectomized dog alive all summer.

Macleod saw the value of the research on his return from Europe, but demanded a re-run to prove the method actually worked. Several weeks later it was clear the second run was

also a success, and he helped publish their results privately in Toronto that November. However, they needed six weeks to extract the isletin, dramatically slowing testing. Banting suggested that they try to use fetal calf pancreas, which had not yet developed digestive glands; he was relieved to find that this method worked well. With the supply problem solved, the next major effort was to purify the protein. In December 1921, Macleod invited the biochemist James Collip to help with this task, and, within a month, he felt ready to test.

On January 11, 1922, Leonard Thompson, a fourteen-year-old diabetic, was given the first injection of insulin. However, the extract was so impure that he suffered a severe allergic reaction, and further injections were canceled. Over the next 12 days, Collip worked day and night to improve the extract, and a second dose injected on the 23rd. This was completely successful, not only in not having obvious side-effects, but in completely eliminating the symptoms of diabetes. However, Banting and Best never worked well with Collip, regarding him as something of an interloper, and Collip left soon after.

Over the spring of 1922, Best managed to improve his techniques to the point where large quantities of insulin could be extracted on demand, but the extract remained impure. However, they had been approached by Eli Lilly and Company with an offer of help shortly after their first publications in 1921, and they took Lilly up on the offer in April. In November, Lilly made a major breakthrough, and were able to produce large quantities of pure insulin. Insulin was offered for sale shortly thereafter.

Nobel Prizes

- Macleod and Banting were awarded the Nobel Prize in Physiology or Medicine in 1923 for the discovery of insulin. Banting, insulted that Best was not mentioned, shared his prize with Best, and MacLeod immediately shared his with Collip. The patent for insulin was sold to the University of Toronto for one dollar.
- The exact sequence of amino acids comprising the insulin molecule, the so-called primary structure, was determined by British molecular biologist Frederick Sanger. It was the first protein to have its structure be completely determined. He was awarded the Nobel Prize in Chemistry in 1958.
- In 1967, after decades of work, Dorothy Crowfoot Hodgkin determined the spatial conformation of the molecule, by means of X-ray diffraction studies. She had been awarded a Nobel Prize in Chemistry in 1964 for the development of crystallography.
- Rosalyn Sussman Yalow received the 1977 Nobel Prize in Medicine for the development of the radioimmunoassay for insulin.

Structure and production

Insulin is synthesized in humans, and other mammals, within the beta cells (^{2}-cells) of the islets of Langerhans in the pancreas. One to three million islets of Langerhans (pancreatic islets) form the endocrine part of the pancreas, which is primarily an exocrine gland. The endocrine part accounts for only 2% of the total mass of the pancreas. Within the islets of Langerhans, beta cells constitute 60–80% of all the cells.

In beta cells, insulin is synthesized from the proinsulin precursor molecule by the action of proteolytic enzymes known as prohormone convertases (PC1 and PC2), as well as the exoprotease carboxypeptidase E. These modifications of proinsulin remove the center portion of the molecule, or C-peptide, from the C- and N- terminal ends of the proinsulin. The remaining polypeptides (51 amino acids in total), the B- and A- chains, are bound together by disulfide bonds. Confusingly, the primary sequence of proinsulin goes in the order "B-C-A", since B and A chains were identified on the basis of mass, and the C peptide was discovered after the others.

Amongst vertebrates, insulin has been highly conserved. Bovine insulin differs from human insulin in only three amino acid residues, and porcine insulin in one residue. Even insulin from some species of fish is also close enough to human insulin to be effective in humans.

Actions on cellular and metabolic level

The actions of insulin on the global human metabolism level include:

- Control of cellular intake of certain substances, most prominently glucose in muscle and adipose tissue (about T of body cells).
- Increase of DNA replication and protein synthesis via control of amino acid uptake.
- Modification of the activity of numerous enzymes (allosteric effect).

The actions of insulin on cells include:

- Increased glycogen synthesis – insulin forces storage of glucose in liver (and muscle) cells in the form of glycogen; lowered levels of insulin cause liver cells to convert glycogen to glucose and excrete it into the blood. This is the clinical action of insulin which is directly useful in reducing high blood glucose levels as in diabetes.
- Increased fatty acid synthesis – insulin forces fat cells to take in blood lipids which are converted to triglycerides; lack of insulin causes the reverse.
- Increased esterification of fatty acids – forces adipose tissue to make fats (ie, triglycerides) from fatty acid esters; lack of insulin causes the reverse.
- Decreased proteinolysis – forces reduction of protein degradation; lack of insulin increases protein degradation.
- Decreased lipolysis – forces reduction in conversion of fat cell lipid stores into blood fatty acids; lack of insulin causes the reverse.
- Decreased gluconeogenesis – decreases production of glucose from various substrates in liver; lack of insulin causes glucose production from assorted substrates in the liver and elsewhere.
- Increased amino acid uptake – forces cells to absorb circulating amino acids; lack of insulin inhibits absorption.
- Increased potassium uptake – forces cells to absorb serum potassium; lack of insulin inhibits absorption.

- Arterial muscle tone – forces arterial wall muscle to relax, increasing blood flow, especially in micro arteries; lack of insulin reduces flow by allowing these muscles to contract.

Regulatory action on blood glucose

Despite long intervals between meals or the occasional consumption of meals with a substantial carbohydrate load (e.g., half a birthday cake or a bag of potato chips), human blood glucose levels normally remain within a narrow range. In most humans this varies from about 70 mg/dl to perhaps 110 mg/dl (3.9 to 6.1 mmol/litre) except shortly after eating when the blood glucose level rises temporarily. This homeostatic effect is the result of many factors, of which hormone regulation is the most important.

It is usually a surprise to realize how little glucose is actually maintained in the blood, and body fluids. The control mechanism works on very small quantities. In a healthy adult male of 75 kg with a blood volume of 5 litres, a blood glucose level of 100 mg/dl or 5.5 mmol/l corresponds to about 5 g (1/5 ounce) of glucose in the blood and approximately 45 g (1½ ounces) in the total body water (which obviously includes more than merely blood and will be usually about 60% of the total body weight in men). A more familiar comparison may help -- 5 grams of glucose is about equivalent to a commercial sugar packet (as provided in many restaurants with coffee or tea).

There are two types of mutually antagonistic metabolic hormones affecting blood glucose levels:

- catabolic hormones (such as glucagon, growth hormone, and catecholamines), which increase blood glucose
- and one anabolic hormone (insulin), which decreases blood glucose

Mechanisms which restore satisfactory blood glucose levels after hypoglycemia must be quick, and effective, because of the immediate serious consequences of insufficient glucose (in the extreme, coma, less immediately dangerously, confusion or unsteadiness, amongst many other effects). This is because, at least in the short term, it is far more dangerous to have too little glucose in the blood than too much. In healthy individuals these mechanisms are indeed generally efficient, and symptomatic hypoglycemia is generally only found in diabetics using insulin or other pharmacologic treatment. Such hypoglycemic episodes vary greatly between persons and from time to time, both in severity and swiftness of onset. In severe cases prompt medical assistance is essential, as damage (to brain and other tissues) and even death will result from sufficiently low blood glucose levels.

Beta cells in the islets of Langerhans are sensitive to variations in blood glucose levels through the following mechanism (see figure to the right):

- Glucose enters the beta cells through the glucose transporter GLUT2
- Glucose goes into the glycolysis and the respiratory cycle where multiple high-energy ATP molecules are produced by oxidation
- Dependent on blood glucose levels and hence ATP levels, the ATP controlled potassium channels (K^+) close and the cell membranes depolarize
- On depolarisation, voltage controlled calcium channels (Ca^{2+}) open and calcium flows into the cells

- An increased calcium level causes activation of phospholipase C, which cleaves the membrane phospholipid phosphatidyl inositol 4,5-bisphosphate into inositol 1,4,5-triphosphate and diacylglycerol.
- Inositol 1,4,5-triphosphate (IP3) binds to receptor proteins in the membrane of endoplasmic reticulum (ER). This allows the release of Ca**2+** from the ER via IP3 gated channels, and further raises the cell concentration of calcium.
- Significantly increased amounts of calcium in the cells causes release of previously synthesised insulin, which has been stored in secretory vesicles
- The calcium level also regulates expression of the insulin gene via the calcium responsive element binding protein (CREB).

This is the main mechanism for release of insulin and regulation of insulin synthesis. In addition some insulin synthesis and release takes place generally at food intake, not just glucose or carbohydrate intake, and the beta cells are also somewhat influenced by the autonomic nervous system. The signalling mechanisms controlling this are not fully understood.

Other substances known which stimulate insulin release are acetylcholine, released from vagus nerve endings (parasympathetic nervous system), cholecystokinin, released by enteroendocrine cells of intestinal mucosa and gastrointestinal inhibitory peptide (GIP). The first of these act similarly as glucose through phospholipase C, while the last acts through the mechanism of adenylate cyclase.

The sympathetic nervous system (via ±2-adrenergic agonists such as norepinephrine) inhibits the release of insulin.

When the glucose level comes down to the usual physiologic value, insulin release from the beta cells slows or stops. If blood glucose levels drop lower than this, especially to dangerously low levels, release of hyperglycemic hormones (most prominently glucagon from Islet of Langerhans' alpha cells) forces release of glucose into the blood from cellular stores, primarily liver cell stores of glycogen. Release of insulin is strongly inhibited by the stress hormone norepinephrine (noradrenaline), which leads to increased blood glucose levels during stress.

Signal transduction

There are special transporter proteins in cell membranes through which glucose from the blood can enter a cell. These transporters are, indirectly, under insulin control in certain body cell types (eg, muscle cells). Low levels of circulating insulin, or its absence, will prevent glucose from entering those cells (eg, in untreated Type 1 diabetes). However, more commonly there is a decrease in the sensitivity of cells to insulin (eg, the reduced insulin sensitivity characteristic of Type 2 diabetes), resulting in decreased glucose absorption. In either case, there is 'cell starvation', weight loss, sometimes extreme. In a few cases, there is a defect in the release of insulin from the pancreas. Either way, the effect is, characteristically, the same: elevated blood glucose levels.

Activation of insulin receptors leads to internal cellular mechanisms which directly affect glucose uptake by regulating the number and operation of protein molecules in the cell membrane which transport glucose into the cell. The genes which specify the proteins which

make up the insulin receptor in cell membranes have been identified and the structure of the interior, cell membrane section, and now, finally after more than a decade, the extra-membrane structure of receptor (Australian researchers announced the work 2Q 2006).

Two types of tissues are most strongly influenced by insulin, as far as the stimulation of glucose uptake is concerned: muscle cells (myocytes) and fat cells (adipocytes). The former are important because of their central role in movement, breathing, circulation, etc, and the latter because they accumulate excess food energy against future needs. Together, they account for about T of all cells in a typical human body.

Hypoglycemia

Although other cells can use other fuels for a while (most prominently fatty acids), neurons depend on glucose as a source of energy in the non-starving human. They do not require insulin to absorb glucose, unlike muscle and adipose tissue, and they have very small internal stores of glycogen. Glycogen stored in liver cells (unlike glycogen stored in muscle cells) can be converted to glucose, and released into the blood, when glucose from digestion is low or absent, and the glycerol backbone in triglycerides can also be used to produce blood glucose. Exhaustion of these sources can, either temporarily or on a sustained basis, if reducing blood glucose to a sufficiently low level, first and most dramatically manifest itself in impaired functioning of the central nervous system – dizziness, speech problems, even loss of consciousness, are not unknown. This is known as hypoglycemia or, in cases producing unconsciousness, "hypoglycemic coma" (formerly termed "insulin shock" from the most common causative agent). Endogenous causes of insulin excess (such as an insulinoma) are very rare, and the overwhelming majority of hypoglycemia cases are caused by human action (e.g. iatrogenic, caused by medicine), and are usually accidental. There have been a few reported cases of murder, attempted murder or suicide using insulin overdoses, but most insulin shocks appear to be due to mismanagement of insulin (didn't eat as much as anticipated, or exercised more than expected), or a mistake (e.g. 20 units of insulin instead of 2).hhhh

Possible causes of hypoglycemia include:

- Oral hypoglycemic agents (e.g., any of the sulfonylureas, or similar drugs, which increase insulin release from beta cells in response to a particular blood glucose level).
- External insulin (usually injected subcutaneously).
- Ingestion of low-carbohydrate sugar substitutes (animal studies show these can trigger insulin release according to a report in Discover magazine August 2005, p18).

Diseases and syndromes

There are several conditions in which insulin disturbance is pathologic:

- Diabetes mellitus – general term referring to all states characterized by hyperglycemia.

  - Type 1 – autoimmune-mediated destruction of insulin producing beta cells in the pancreas resulting in absolute insulin deficiency.
  - Type 2 – multifactoral syndrome with combined influence of genetic susceptibility and influence of environmental factors, the best known being obesity, age, and physical inactivity, resulting in insulin resistance in cells requiring insulin for glucose absorption. This form of diabetes is strongly inherited.
  - Other types of impaired glucose tolerance (see the diabetes article).
- Insulinoma or reactive hypoglycemia.
- Metabolic syndrome – a precondition first called Metabolic Syndrome X by Gerald Reaven, and sometimes called prediabetes. It is characterized by elevated blood pressure, dyslipidemia (disturbances in blood cholesterol forms and other blood lipids), and increased waist circumference (at least in populations in much of the developed world). The basic underlying cause is insulin resistance, a diminished capacity for insulin response in some tissues (eg, muscle, fat, liver) to respond to insulin. Untreated, Metabolic Syndrome can lead to morbidities such as essential hypertension, obesity, Type 2 diabetes, and cardiovascular disease (CVD).
- Polycystic ovary syndrome – a complex syndrome in women in the reproductive years where there is anovulation and androgen excess commonly displayed as hirsutism. In many cases of PCOS insulin resistance is present.

As a medication

Principles

Insulin is absolutely required for all animal (including human) life. The mechanism is almost identical in nematode worms (e.g. C. elegans), fish, and in mammals. In humans, insulin deprivation due to the removal or destruction of the pancreas leads to death in days or at most weeks. Insulin must be administered to patients in whom there is a lack of the hormone for this, or any other, reason. Clinically, this is called diabetes mellitus type 1.

The initial source of insulin for clinical use in humans was from cow, horse, pig or fish pancreases. Insulin from these sources is effective in humans as it is nearly identical to human insulin (three amino acid difference for bovine insulin, one amino acid difference for porcine). Insulin is obviously a protein which has been very strongly conserved across evolutionary time. Differences in suitability of beef, pork, or fish insulin preparations for particular patients have been primarily the result of preparation purity and of allergic reactions to assorted non-insulin substances remaining in those preparations. Purity has improved more or less steadily since the 1920s, but allergic reactions have continued though slowly reducing in severity. Insulin production from animal pancreases was widespread for decades, but there are very few patients today relying on insulin from these sources.

Human insulin is now manufactured for widespread clinical use using genetic engineering techniques, which significantly reduces impurity reaction problems. Eli Lilly marketed the first such insulin, Humulin, in 1982. Humulin was the first medication

produced using modern genetic engineering techniques, in which actual human DNA is inserted into a host cell (E. coli in this case). The host cells are then allowed to grow and reproduce normally, and due to the inserted human DNA, they produce actual human insulin.

Genentech developed the technique Lilly used to produce Humulin. Novo Nordisk has also developed a genetically engineered insulin independently. Most insulins used clinically are produced this way, for they avoid most of the allergic reaction problem.

Since January 2006, all insulins distributed in the U.S. and some other countries are human insulins or their analogs. A special FDA importation process is required to obtain beef or pork insulin for use in the U.S., though there may be some remaining stocks of pork insulin made by Lilly in 2005 or earlier.

Modes of administration

Unlike many medicines, insulin cannot be taken orally; like other proteins in the gastrointestinal tract, it is reduced to its amino acid components, whereupon all 'insulin activity' is lost. There is research underway to develop methods of protecting insulin so that it can be taken orally, but none has yet reached clinical use (see oral insulin). Instead insulin is usually taken as subcutaneous injections by single-use syringes with needles, an insulin pump or by repeated-use insulin pens with needles.

There are several problems with insulin as a clinical treatment for diabetes:

- Mode of administration.
- Selecting the 'right' dose and timing.
- Selecting an appropriate insulin preparation (typically on 'speed of onset and duration of action' grounds).
- Adjusting dosage and timing to fit food amounts and types.
- Adjusting dosage and timing to fit exercise undertaken.
- Adjusting dosage, type, and timing to fit other conditions as for instance the increased stress of illness.
- The dosage is non-physiological in that a subcutaneous bolus dose of insulin alone is administered instead of combination of insulin and C-peptide being released gradually and directly into the portal vein.
- It is simply a nuisance for patients to inject themselves once or several times a day.
- It may be dangerous in the case of mistake (most especially 'too much' insulin).

There have been attempts to improve upon this mode of administering insulin, as many people find injection awkward and painful. One alternative is jet injection (also sometimes used for vaccinations), which has different insulin delivery peaks and durations as compared to needle injection. Some diabetics find control possible with jet injectors, but not with hypodermic injection. There are also 'insulin pumps' of various types which are 'electrical injectors' attached to a semi-permanently implanted needle (i.e. a catheter). Some who cannot achieve adequate glucose control by conventional injection (or sometimes jet injection) are able to do so with the appropriate pump.

An insulin pump is a reasonable solution for some. However there are limitations - cost, the potential for hypoglycemic episodes, catheter problems, and, so far, no approvable means of controlling insulin delivery in the field based on current blood glucose levels. If too much insulin is delivered, or the patient eats less than normal, there will be hypoglycemia. On the other hand, if too little insulin is delivered, there will be hyperglycemia. Both of these can lead to life-threatening conditions. In addition, indwelling catheters pose the risk of infection and ulceration. However, that risk can be minimized by keeping catheter sites clean. Thus far, insulin pumps require care and effort to use correctly. However, some diabetics are able to keep their glucose in reasonable control only on a pump.

Researchers have produced a watch-like device that tests for blood glucose levels through the skin and administers corrective doses of insulin through pores in the skin. Both electricity and ultrasound have been found to make the skin temporarily porous. The insulin administration aspect remains experimental, but the blood glucose test aspect of 'wrist appliances' is commercially available.

Another 'improvement' would be to avoid periodic insulin administration by a self-regulating insulin source, for instance, pancreatic, or beta cell, transplantation. Transplantation of an entire pancreas (as an individual organ) is difficult, and is not common. Generally, it is performed in conjunction with liver or kidney transplant. However, transplantation of only pancreatic beta cells is a possibility. It has been highly experimental (for which read 'prone to failure') for many years, but some researchers in Alberta, Canada, have developed techniques with a high initial success rate (about 90% in one group). Beta cell transplant may become practical and common in the near future. Additionally, some researchers have explored the possibility of transplanting genetically engineered non-beta cells to secrete insulin.[1] Clinically testable results are far from realization. Several other non-transplant methods of automatic insulin delivery are being developed in research labs, but none is close to clinical approval.

Inhaled insulin is under investigation, as are several other insulin administration techniques. Currently the only inhalable insulin approved by the Food and Drug Administration [1]is Exubera. Inhaled insulin has been shown to have similar efficacy to injected insulin, both in terms of controlling glucose levels and blood half-life. When patients were switched from injected to inhaled insulin, no significant difference was found in HBA1c levels over three months. Patients showed no significant weight gain or pulmonary function over the length of the trial, when compared to the baseline.[2] However following its commercial launch in 2005 into the UK, it has not (as of July 2006) been recommended by National Institute for Health and Clinical Excellence for routine use, except in cases where there is "proven injection phobia diagnosed by a psychiatrist or psychologist".[3]

An additional method of administration of insulin to diabetics is pulsatile insulin. In this method insulin is pulsed into the patient, mimicking the physiological secretions of insulin by the pancreas.

Dosage and timing

The central problem for those requiring external insulin is picking the right dose of insulin and the right timing.

Physiological regulation of blood glucose, as in the non-diabetic, would be best. Increased blood glucose levels after a meal is a stimulus for prompt release of insulin from the pancreas. The increased insulin level causes glucose absorption and storage in cells, reducing glycogen to glucose conversion, reducing blood glucose levels, and so reducing insulin release. The result is that the blood glucose level rises somewhat after eating, and within an hour or so returns to the normal 'fasting' level. Even the best diabetic treatment with human insulin, however administered, falls short of normal glucose control in the non-diabetic.

Complicating matters is that the composition of the food eaten (see glycemic index) affects intestinal absorption rates. Glucose from some foods is absorbed more (or less) rapidly than the same amount of glucose in other foods. And, fats and proteins both cause delays in absorption of glucose from carbohydrate eaten at the same time. As well, exercise reduces the need for insulin even when all other factors remain the same, since working muscle has some ability to take up glucose without the help of insulin.

It is, in principle, impossible to know for certain how much insulin (and which type) is needed to 'cover' a particular meal in order to achieve a reasonable blood glucose level within an hour or two after eating. Non-diabetics' beta cells routinely and automatically manage this by continual glucose level monitoring and insulin release. All such decisions by a diabetic must be based on experience and training (ie, at the direction of a physician or PA, or in some places a specialist diabetic educator) and, further, specifically based on the individual experience of the patient. It is not straightforward and should never be done by habit or routine, but with care can be done quite successfully in practice.

For example, some diabetics require more insulin after drinking skim milk than they do after taking an equivalent amount of fat, protein, carbohydrate, and fluid in some other form. Their particular reaction to skimmed milk is different from other diabetics', but the same amount of whole milk is likely to cause a still different reaction even in that person. Whole milk contains considerable fat while skimmed milk has much less. It is a continual balancing act for all diabetics, especially for those taking insulin.

Insulin dependent diabetics require a base level of insulin (Basal Insulin), as well as extra short acting insulin to cope with meals (Bolus Insulin). Maintaining the basal rate and the bolus rate is a continuous balancing act that all insulin diabetics have to manage each day. This is normally achieved through regular blood tests, although there is work being undertaken on continuous blood sugar testing equipment.

It is important to notice that diabetics generally need more insulin than the usual -- not less -- during physical stress like infections or surgeries.

Types

Medical preparations of insulin (from the major suppliers — Eli Lilly and Novo Nordisk — or from any other) are never just 'insulin in water'. Clinical insulins are specially prepared mixtures of insulin plus other substances. These delay absorption of the insulin, adjust the pH of the solution to reduce reactions at the injection site, and so on.

The insulin molecules in an insulin analog is slightly modified so that they are:

- Absorbed rapidly enough to mimic real beta cell insulin (Lilly's is lispro, Novo Nordisk's is aspart).

- Steadily absorbed after injection instead of having a 'peak' followed by a more or less rapid decline in insulin action (Novo Nordisk' version is Insulin detemir and Aventis' version is Insulin glargine).
- All while retaining insulin action in the human body.

The management of choosing insulin type and dosage / timing should be done by an experienced medical professional working with the diabetic.

Allowing blood glucose levels to rise, though not to levels which cause acute hyperglycemic symptoms, is not a sensible choice. Several large, well designed, long term studies have conclusively shown that diabetic complications decrease markedly, linearly, and consistently as blood glucose levels approach 'normal' patterns over long periods. In short, if a diabetic closely controls blood glucose levels (ie, on average, both over days and weeks, and avoiding too high peaks after meals) the rate of diabetic complications goes down. If glucose levels are very closely controlled, that rate can even approach 'normal'. The chronic diabetic complications include cerebrovascular accidents (CVA or stroke), heart attack, blindness (from proliferative diabetic retinopathy), other vascular damage, nerve damage from diabetic neuropathy, or kidney failure from diabetic nephropathy. These studies have demonstrated beyond doubt that, if it is possible for a patient, so-called intensive insulinotherapy is superior to conventional insulinotherapy. However, close control of blood glucose levels (as in intensive insulinotherapy) does require care and considerable effort, for hypoglycemia is dangerous and can be fatal.

A good measure of long term diabetic control (over approximately 90 days in most people) is the serum level of glycosylated hemoglobin (HbA1c). A shorter term integrated measure (over two weeks or so) is the so-called fructosamine level, which is a measure of similarly glyclosylated proteins (chiefly albumin) with a shorter half life in the blood. There is a commercial meter available which measures this level in the field.

The commonly used types of insulin are:

- Quick-acting, such as insulin lispro -- begins to work within 5 to 15 minutes and is active for 3 to 4 hours.
- Short-acting, such as regular insulin -- starts working within 30 minutes and is active about 5 to 8 hours.
- Intermediate-acting, such as NPH, or lente insulin -- starts working in 1 to 3 hours and is active 16 to 24 hours.
- Long-acting, such as ultralente insulin -- starts working in 4 to 6 hours, and is active 24 to 28 hours, and Insulin glargine or Insulin detemir -- both start working within 1 to 2 hours and continue to be active, without peaks or dips, for about 24 hours.
- A mixture of NPH and regular insulin -- starts working in 30 minutes and is active 16 to 24 hours. There are several variations with different proportions of the mixed insulins.

Abuse

There are reports that some patients abuse insulin by injecting larger doses that lead to mild hypoglycemic states. This is extremely dangerous. Severe acute or prolonged hypoglycemia can result in brain damage or death.

On July 23, 2004, news reports claim that a former spouse of a prominent international track athlete said that, among other drugs, the ex-spouse had used insulin as a way of 'energizing' the body. The intended implication would seem to be that insulin has effects similar to those alleged for some steroids. This is not so; eighty years of insulin use has given no reason to believe it to be in any respect a performance enhancer for non diabetics. Improperly treated diabetics are, to be sure, more prone than others to exhaustion and tiredness, and in some of these cases, proper administration of insulin can relieve such symptoms. However, insulin is not, chemically or clinically, a steroid, and its use in non diabetics is dangerous and always an abuse outside of a well-equipped medical facility.

"Game of Shadows," by reporters Mark Fainaru-Wada and Lance Williams, includes allegations that San Francisco Giant, Barry Bonds, used insulin in the apparent belief that it would increase the effectiveness of the growth hormone he was (also alleged to be) taking. On top of this, non-prescribed insulin is a banned drug at the Olympics and other global competitions.

Timeline

- 1922 Banting and Best use bovine insulin extract in human

1923 Eli Lilly produces commercial quantities of bovine insulin
1923 Hagedorn founds the Nordisk Insulinlaboratorium in Denmark -- forerunner of Novo Nordisk
1926 Nordisk receives a Danish charter to produce insulin as a non profit
1936 Canadians D.M. Scott, A.M. Fisher formulate a zinc insulin mixture and license to Novo
1936 Hagedorn discovers that adding protamine to insulin prolongs the effect of insulin
1946 Nordisk formulates Isophane® porcine insulin aka Neutral Protamine Hagedorn or NPH insulin
1946 Nordisk crystallizes a protamine and insulin mixture
1950 Nordisk markets NPH insulin
1953 Novo formulates Lente® porcine and bovine insulins by adding zinc for longer lasting insulin
1973 Purified monocomponent (MC) insulin is introduced
1978 Genentech produces human insulin in Escheria coli bacteria using recombinant DNA
1981 Novo Nordisk chemically and enzymatically converts bovine to human insulin
1982 Genentech human insulin (above) approved
1983 Eli Lilly produces recombinant human insulin, Humulin®
1985 Axel Ullrich sequences the human insulin receptor
1988 Novo Nordisk produces recombinant human insulin
1996 Lilly Humalog® "lyspro" insulin analogue approved

2004 Aventis Lantus® "glargine" insulin analogue approved for clinical use [citation needed]
2006 Novo Nordisk Levemir® "detemir" approved for clincal use in the US.

See also

- Forms of diabetes mellitus
  - Diabetes mellitus

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Footnotes

1. ^ **FDA approval of** *Exubera* **inhaled insulin** http://www.fda.gov/bbs/topics/news/2006/NEW01304.html

2. ^ Cefalu W, Skyler J, Kourides I, Landschulz W, Balagtas C, Cheng S, Gelfand R (2001). "Inhaled human insulin treatment in patients with type 2 diabetes mellitus.". Ann Intern Med *134* (3): 203-7. PMID 11177333.

3. ^ **NICE (June 21 2006).** Diabetes (type 1 and 2), Inhaled Insulin - Appraisal Consultation Document (second)**. Retrieved on 2006-07-26.**

Meglitinides

The *meglitinide* class of drugs treat diabetes type 2 by blocking the potassium channels in beta cells, which closes the ATP-dependent potassium channels and opens the cells' calcium channels. The resulting calcium influx causes the cells to secrete insulin.

Drugs

The main branded drug in the meglitinide class is Novo Nordisk's Prandin(repaglinide), which gained FDA approval in 1997. Another type of drug in this class is nateglinide (Starlix)

These drugs should be taken 0-30 minutes prior to eating. Follow the instructions given to you by your physician/nurse.

Side-effects

Side effects include weight gain and hypoglycemia. While the potential for hypoglycemia is less than for those on sulfonylureas, it is still a serious potential side effect that can be life-threatening. Patients on this medication should know the signs and symptoms of hypoglycemia and appropriate action to take.

Sulfonylureas

Sulfonylurea derivatives are a class of antidiabetic drugs that are used in the management of diabetes mellitus type 2 ("adult-onset"). They act by increasing insulin release from the beta cells in the pancreas.

Drugs in this class

First generation:

- Chlorpropamide
- Tolbutamide
- Tolazamide

Second generation:

- Glipizide
- Gliclazide
- Glibenclamide (glyburide)
- Glimepiride
- Gliquidone

Chemistry

Please see individual members of the class for their chemical structure

All sulfonylureas have a central phenyl ring with two branching chains

Pharmacology

Method of action

Sulfonylureas bind to an ATP-dependent K+ channel on the cell membrane of pancreatic beta cells. This inhibits a tonic, hyperpolarizing outflux of potassium, which causes the electric potential over the membrane to become more positive. This depolarization opens voltage-gated Ca**2+** channels. The rise in intracellular calcium leads to increased fusion of insulin granulae with the cell membrane, and therefore increased secretion of (pro)insulin.

There is some evidence that sulfonylureas also sensitize ²-cells to glucose, that they limit glucose production in the liver, that they decrease lipolysis (breakdown and release of fatty acids by adipose tissue) and decrease clearance of insulin by the liver.

Pharmacokinetics

Various sulfonylureas have different pharmacokinetics. The choice depends on the propensity of the patient to develop hypoglycemia - long-acting sulfonylureas with active metabolites can induce hypoglycemia. They can, however, help achieve glycemic control when tolerated by the patient. The shorter-acting agents may not control blood sugar levels adequately.

Due to varying half-life, some drugs have to be taken twice (e.g. tolbutamide) or three times a day rather than once (e.g. glimepiride). The short-acting agents may have to be taken about 30 minutes before the meal, to ascertain maximum efficacy when the food leads to increased blood glucose levels.

Some sulfonylureas are metabolised by liver metabolic enzymes (cytochrome P450) and inducers of this enzyme system (such as the antibiotic rifampicin) can therefore increase the clearance of sulfonylureas. In addition, because some sulfonylureas are bound to plasma proteins, use of drugs that also bind to plasma proteins can release the sulfonylureas from their binding places, leading to increased clearance.

Uses

Sulfonylureas are used almost exclusively in diabetes mellitus type 2. Other types of diabetes generally do not respond to sulfonylurea therapy, or (in diabetes of pregnancy) there are other contraindications.

Although for many years sulfonylureas were the first drugs to be used in new cases of diabetes, in the 1990s it was discovered that obese patients might benefit more from metformin.

In about 10% of patients, sulfonylureas alone are ineffective in controlling blood glucose levels. Addition of metformin or a thiazolidinedione may be necessary, or (ultimately) insulin. Triple therapy of sulfonylureas, a biguanide (metformin) and a thiazolidinedione is generally discouraged, but some doctors prefer this combination over resorting to insulin.

Side-effects and cautions

Sulfonylureas, as opposed to metformin and the thiazolidinediones, can induce hypoglycemia when insulin production overshoots. It is treated with sugary food, or (in the

case of hypoglycemic coma) with intravenous dextrose. The best way to prevent this side-effect is to choose the lowest possible dose that adequately controls glucose levels.

Like insulin, sulfonylureas can induce weight gain, mainly as a result of fluid retention and improvement of osmotic diuresis. Other side-effects are: abdominal upset, headache and hypersensitivity reactions.

Sulfonylureas are potentially teratogenic and cannot be used in pregnancy or in patients who intend to get pregnant. Impairment of liver or kidney function increase the risk of hypoglycemia, and are contraindications. As other anti-diabetic drugs cannot be used either under these circumstances, insulin therapy is the only option in pregnancy and hepatic and renal failure.

Second generation sulfonylureas have increased potency by weight, compared to first generation sulfonylureas. They have decreased side effects but an increased cost.

Some rare cases of Type 1 diabetes have been found to react to this drug in a positive way

History

Sulfonylureas were discovered by the chemist Marcel Janbon and co-workers, who were studying sulfonamide antibiotics and discovered that the compound sulfonylurea induced hypoglycemia in animals (see also Patlak 2002). It was reported in: Janbon M, Chaptal J, Vedel A, Schaap J. Accidents hypoglycémiques graves par un sulfamidothiodiazol (le VK 57 ou 2254 RP). Montpellier Med. 1942;441:21-22.

See also

- diabetes mellitus
- thiazolidinediones

References

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Thiazolidinediones

The medication class of *thiazolidinedione* was introduced in the late 1990s as an adjunctive therapy for diabetes mellitus (type 2) and related diseases.

Mode of action

Thiazolidinediones or TZDs act by binding to PPARs (peroxisome proliferator-activated receptors), a group of receptor molecules inside the cell nucleus, specifically PPAR[3] (gamma). The normal ligands for these receptors are free fatty acids (FFAs) and eicosanoids.

When activated, the receptor migrates to the DNA, activating transcription of a number of specific genes.

Genes upregulated by PPAR^3 can be found in the main article on peroxisome proliferator-activated receptors.

By activating PPAR^3:

- insulin resistance is decreased

adipocyte differentiation is modified
VEGF-induced angiogenesis is inhibited (abstract).
Leptin levels decrease (leading to an increased appetite)
Levels of certain interleukins (e.g. IL-6) fall
Adiponectin levels rise

Members of the class

These include:

- rosiglitazone (Avandia)

pioglitazone (Actos)

Troglitazone was withdrawn from the market due to an increased incidence of drug-induced hepatitis in patients who were using the drug. It is now common practice that liver enzymes are monitored during the first year of treatment with the "newer" thiazolidinediones.

Experimental agents include MCC-555, a powerful antidiabetic agent and the early non-marketed thiazolidinedione ciglitazone.

Uses

The only registered use of the thiazolidinediones is in diabetes mellitus type 2.

It is being investigated experimentally in polycystic ovary syndrome (PCOS) and non-alcoholic steatohepatitis (NASH).

Several forms of lipodystrophy cause insulin resistance, which has responded favorably to thiazolidinediones.

Side effects and contraindications

The withdrawal of troglitazone has led to concerns of other thiazolidinediones increasing the risk of hepatitis. Guidelines now mention that for the first year of thiazolidinedione therapy, a two- or three-monthly check of liver enzymes is conducted to ascertain that no liver damage is occurring.

The main side effect of all thiazolidinediones is fluid retention, leading to edema, weight gain, and potentially aggravating heart failure. Therefore, thiazolidinediones cannot be prescribed in patients with decreased ventricular function (NYHA grade III and IV heart failure).

Anti-inflammatory agents

Anti-inflammatory refers to the property of a substance or treatment that reduces inflammation. Anti-inflammatory drugs make up one half of analgesics, remedying pain by reducing inflammation as opposed to opioids which affect the brain.

Steroidal anti-inflammatory drugs

Many steroids, specifically glucocorticoids, reduce inflammation by binding to cortisol receptors. These drugs are often referred to as corticosteroids, though that is a larger category.

Non-steroidal anti-inflammatory drugs

Non-steroidal anti-inflammatory drugs (NSAIDs), alleviate pain by counteracting the cyclooxygenase (COX) enzyme. On its own COX enzyme synthesizes prostaglandins, creating inflammation. In whole the NSAIDs prevent the prostaglandins from ever being synthesized, reducing or eliminating the pain.

In addition to medical drugs, many herbs have anti-inflammatory qualities, including hyssop, Arnica montana which contains helenalin, a sesquiterpene lactone, and willow bark, which contains salicylic acid, a substance related to the active ingredient in aspirin.

On the other hand, there are analgesics like paracetamol, called acetaminophen in the U.S. and sold under the brand name of Tylenol, which are commonly associated with anti-inflammatory drugs but which have no anti-inflammatory effects.

Some are concerned about the long term usage of NSAIDs as they cause gastric erosions which can become stomach ulcers and in extreme cases result in death. The risk of death as a result of use of NSAIDs is 1 in 10,000 for young adults aged 16-45. The risk increases ten fold for those over 75.

Ice treatment

Applying ice to a tissue injury has an anti-inflammatory effect and is often suggested as an injury treatment and pain management technique for athletes.

Anti-inflammatory Foods

Due to concerns over the gastric problems caused by NSAIDs researchers are turning to more natural solutions to dealing with the problem of inflammation. One ingredient with a great future potential is capsaicin, a naturally occurring ingredient in chili peppers. Studies have shown some success in the control of pain and inflammation when capsaicin is applied topically.

Others advocate the consumption of anti-inflammatory foods as a means of controlling inflammation. Anti-inflammatory foods include most colorful fruits and vegetables, oily fish and certain nuts, seeds, herbs and spices. Those following an anti-inflammatory diet will

avoid refined oils and sugars, and show a preference for anti-inflammatory foods in their meal choices. Several types of "Smoker's Paradoxes" [29], i.e. cases where smoking appears to have specific beneficial effects, have been observed; often the actual mechanism remains undetermined. For instance, recent studies suggest that smokers require less frequent repeated revascularization after percutaneous coronary intervention (PCI) [29], [30]. Smoking appears to interfere with development of Kaposi's sarcoma [31], breast cancer among women carrying the very high risk BRCA gene [32], preeclampsia [33], and atopic disorders such as allergic asthma [34]. A plausible mechanism of action in these cases may be the nicotine in tobacco smoke acting as an anti-inflammatory agent [35] and interfering with the disease process.

Glucocorticoids

Glucocorticoids are a class of steroid hormones characterised by an ability to bind with the cortisol receptor and trigger similar effects. Glucocorticoids are distinguished from mineralocorticoids and sex steroids by the specific receptors, target cells, and effects. Technically, the term corticosteroid refers to both glucocorticoids and mineralocorticoids, but is often used as a synonym for glucocorticoid.

Cortisol (or hydrocortisone) is the most important human glucocorticoid. It is essential for life and regulates or supports a variety of important cardiovascular, metabolic, immunologic, and homeostatic functions. Glucocorticoid receptors are found in the cells of almost all vertebrate tissues.

Effects

The name *glucocorticoid* derives from early observations that these hormones were involved in glucose metabolism. In the fasted state, cortisol stimulates several processes that collectively serve to increase and maintain normal concentrations of glucose in blood. These effects include:

- Stimulation of gluconeogenesis, particularly in the liver: This pathway results in the synthesis of glucose from non-hexose substrates such as amino acids and lipids and is particularly important in carnivores and certain herbivores. Enhancing the expression of enzymes involved in gluconeogenesis is probably the best known metabolic function of glucocorticoids.
- Mobilization of amino acids from extrahepatic tissues: These serve as substrates for gluconeogenesis.
- Inhibition of glucose uptake in muscle and adipose tissue: A mechanism to conserve glucose.
- Stimulation of fat breakdown in adipose tissue: The fatty acids released by lipolysis are used for production of energy in tissues like muscle, and the released glycerol provide another substrate for gluconeogenesis.

Glucocorticoids have potent anti-inflammatory and immunosuppressive properties. This is particularly evident when they are administered at pharmacological doses, but also is important in normal immune responses. As a consequence, glucocorticoids are widely used as drugs to treat inflammatory conditions such as arthritis or dermatitis, and as adjunction therapy for conditions such as autoimmune diseases.

Glucocorticoids have multiple effects on fetal development. An important example is their role in promoting maturation of the lung and production of the surfactant necessary for extrauterine lung function. Mice with homozygous disruptions in the corticotropin-releasing hormone gene (see below) die at birth due to pulmonary immaturity.

Excessive glucocorticoid levels resulting from administration as a drug or hyperadrenocorticism have effects on many systems. Some examples include inhibition of bone formation, suppression of calcium absorption (both of which can lead to osteoporosis), delayed wound healing, muscle weakness and increased risk of infection. These observations suggest a multitude of less dramatic physiologic roles for glucocorticoids.

Mode of action

Glucocorticoids bind to the cytosolic glucocorticoid receptor. This type of receptor gets activated upon ligand binding. After a hormone binds to the corresponding receptor, the newly formed receptor-ligand complex translocates itself into the cell nucleus, where it binds to many glucocorticoid response elements (GRE) in the promoter region of the target genes. The opposite mechanism is called *transrepression*. The activated hormone receptor interacts with specific transcription factors and prevents the transcription of targeted genes. Glucocorticoids are able to prevent the transcription of any of immune genes, including the IL-2 gene.

The ordinary glucocorticoids do not distinguish among transactivation and transrepression and influence both the "wanted" immune and "unwanted" genes regulating the metabolic and cardiovascular functions. Currently, intensive research is aimed at discovering selectively acting glucocorticoids that will be able to repress only the immune system.

Pharmacologic properties

A variety of *synthetic glucocorticoids,* some far more potent than cortisol, have been created for therapeutic use. They differ in the pharmacokinetics (absorption factor, half-life, volume of distribution, clearance) and in pharmacodynamics (for example the capacity of mineralocorticoid activity: retention of sodium ($Na+$) and water; see also: renal physiology). Because they absorb well through the intestines, they are primarily administered per os (by mouth), but also by other ways like topically on skin. More than 90 per cent of them bind different plasma proteins, however with a different binding specificity. Endogenous glucocorticoids and some synthetic corticoids have high affinity to the protein transcortin (also called CBG, corticosteroid binding protein), while all of them bind albumin. In the liver, they quickly metabolise by conjugation with a sulfate or glucuronic acid and are secreted in the urine.

Glucocorticoid potency, duration of effect, and overlapping mineralocorticoid potency varies (Table).

Comparative steroid potencies

Name	Glucocorticoid potency	Mineralocorticoid potency	Duration of action ($t_{1/2}$ in hours)
Hydrocortisone	1	1	8
Cortisone acetate	0.8	0.8	oral 8, intramuscular 18+
Prednisone	3.5-5	0.8	16-36
Prednisolone	4	0.8	16-36
Methylprednisolone	5-7.5	0.5	18-40
Dexamethasone	25-80	0	36-54
Betamethasone	25-30	0	36-54
Triamcinolone	5	0	12-36
Beclometasone	8 puffs 4 times a day equals 14 mg oral prednisone once a day	-	-
Fludrocortisone acetate	15	200	-
Deoxycorticosterone acetate (DOCA)	0	20	-
Aldosterone	0.3	200-1000	-

Cortisol (hydrocortisone) is the standard of comparison for glucocorticoid potency. Hydrocortisone is the name used for pharmaceutical preparations of cortisol. Data refer to oral dosing, except when mentioned. Note that oral potency may be less than parenteral potency because significant amounts (up to 50% in some cases) may not be absorbed from the intestine. Note that fludrocortisone, DOCA, and aldosterone are not considered glucocorticoids and are included in this table to provide perspective on mineralocorticoid potency.

Physiologic replacement of glucocorticoid

Any glucocorticoid can be given in a dose that provides approximately the same glucocorticoid effects as normal cortisol production; this is referred to as physiologic, replacement, or maintenance dosing. This is approximately 6-12 mg/m**2**/day (m**2** refers to body surface area (BSA) and is a measure of body size; an average man is 1.7 m**2**).

Medical uses and effects of high dose glucocorticoids

In much higher doses (termed pharmacologic doses), glucocorticoids are used to suppress various allergic, inflammatory, and autoimmune disorders. They are also administered as posttransplantory immunosuppressants to prevent the acute transplant rejection and the graft-versus-host disease. Nevertheless, they do not prevent an infection and also inhibit later reparative processes.

Some drugs used are cortisol (hydrocortisone), prednisone and dexamethasone.

Immunosuppressive mechanism

Glucocorticoids suppress the cell-mediated immunity. They act by inhibiting genes that code for the cytokines IL-1, IL-2, IL-3, IL-4, IL-5, IL-6, IL-8 and TNF-[3], the most important of which is the IL-2. Smaller cytokine production reduces the T cell proliferation.

Glucocorticoids also suppress the humoral immunity, causing B cells to express smaller amounts of IL-2 and of IL-2 receptors. This diminishes both B cell clone expansion and antibody synthesis. The diminished amounts of IL-2 also causes less T lymphocyte cells to be activated.

Since glucocorticoid is a steroid, it regulates transcription factors; another factor it down regulates is the expression of Fc receptors on macrophages, so there is a decreased phagocytosis of opsonised cells.

Antiinflammatory effects

Glucocorticoids influence all types of inflammatory events, no matter what their cause. They induce the lipocortin-1 (annexin-1) synthesis, which then binds to cell membranes preventing the phospholipase A2 from coming into contact with its substrate arachidonic acid. This leads to diminished eicosanoid production. The cyclooxygenase (both COX-1 and COX-2) expression is also suppressed, potentiating the effect. In other words, the two main products in inflammation Prostaglandins and Leukotrienes are inhibited by the action of Glucocorticoids.

Glucocorticoids also stimulate the lipocortin-1 escaping to the extracellular space, where it binds to the leukocyte membrane receptors and inhibits various inflammatory events: epithelial adhesion, emigration, chemotaxis, phagocytosis, respiratory burst and the release of various inflammatory mediators (lysosomal enzymes, cytokines, tissue plasminogen activator, chemokines etc.) from neutrophils, macrophages and mastocytes.

Side effects

Glucocorticoid drugs currently being used act nonselectively, so in the long run they may impair many healthy anabolic processes. To prevent this, much research has been focused recently on the elaboration of selectively acting glucocorticoid drugs. These are the side effects that could be prevented:

- immunosuppression

hyperglycemia due to increased gluconeogenesis, insulin resistance and impaired glucose tolerance ("steroid diabetes"); caution in those with diabetes mellitus

increased skin fragility, easy bruising

reduced bone density (osteoporosis, higher fracture risk, slower fracture repair)

weight gain due to increased visceral and truncal fat deposition (central obesity) and appetite stimulation

adrenal insufficiency (if used for long time and stopped suddenly without a taper)

muscle breakdown (proteolysis), weakness; reduced muscle mass and repair
expansion of malar fat pads and dilation of small blood vessels in skin
anovulation, irregularity of menstrual periods
growth failure, pubertal delay
increased plasma amino acids, increased urea formation; negative nitrogen balance
excitatory effect on central nervous system

In high doses, hydrocortisone (cortisol) and those glucocorticoids with appreciable mineralocorticoid potency can exert a mineralocorticoid effect as well, although in physiologic doses this is prevented by rapid degradation of cortisol by 11^2-hydroxysteroid dehydrogenase isoenzyme 2 (11^2-HSD2) in mineralocorticoid target tissues. Mineralocorticoid effects can include salt and water retention, extracellular fluid volume expansion, hypertension, potassium depletion, and metabolic alkalosis.

The combination of clinical problems produced by prolonged, excess glucocorticoids, whether synthetic or endogenous, is termed Cushing's syndrome.

Adrenal suppression and withdrawal

In addition to the effects listed above, use of high dose steroids for more than a week begins to produce suppression of the patient's adrenal glands because the exogenous glucocorticoids suppress hypothalamic corticotropin releasing hormone (CRH) and pituitary adrenocorticotropic hormone (ACTH). With prolonged suppression the adrenal glands atrophy (physically shrink) and can take months to recover full function after discontinuation of the exogenous glucocorticoid.

During this recovery time, the patient is vulnerable to adrenal insufficiency during times of stress, such as illness. While there is wide individual variation in suppressive dose and time for adrenal recovery, clinical guidelines have been devised to estimate potential adrenal suppression and recovery, to reduce risk to the patient. The following is one example, but many variations exist or may be appropriate in individual circumstances.

- If a patient has been receiving daily high doses for 5 days or less, they can be abruptly stopped (or reduced to physiologic replacement if patient is adrenal deficient). Full adrenal recovery can be assumed to occur by a week afterward.
- If high doses were used for 6-10 days, reduce to replacement dose immediately and taper over 4 more days. Adrenal recovery can be assumed to occur within 2-4 weeks of completion of steroids.
- If high doses were used for 11-30 days, cut immediately to twice replacement, and then by 25% every 4 days. Stop entirely when dose is less than half of replacement. Full adrenal recovery should occur within 1-3 months of completion of withdrawal.
- If high doses were used more than 30 days, cut dose immediately to twice replacement, and reduce by 25% each week until replacement is reached.
- Then change to oral hydrocortisone or cortisone as a single morning dose, and gradually decrease by 2.5 mg each week. When a.m. dose is less than

replacement, the return of normal basal adrenal function may be documented by checking 0800 cortisol levels prior to the morning dose; stop drugs when 0800 cortisol is 10 ¼g/dl. It is difficult to predict the time to full adrenal recovery after prolonged suppressive exogenous steroids; some people may take nearly a year.

- Flare-up of the underlying condition for which steroids are given may require a more gradual taper than outlined above.

See also

- Immunosuppressive drug

Cortisol

Systematic (IUPAC) name

11,17,21-trihydroxy-,(11beta)-pregn-4-ene-3,20-dione

Identifiers

CAS number 50-23-7

ATC code H02AB09 (and others)

PubChem 5754

Chemical data

Mol. weight 362.465

Therapeutic considerations

Pregnancy cat. C

Routes Oral tablets, intravenously, topical

Cortisol is a corticosteroid hormone produced by the adrenal cortex that is involved in the response to stress; it increases blood pressure, blood sugar levels, may cause infertility in women, and suppresses the immune system. In pharmacology, cortisol is referred to as Hydrocortisone, and is used to treat allergies and inflammation.

Synthesis

Cortisol is synthesized from pregnenolone. The change involves hydroxylation of C-11, C-17, and C-21, the oxidation of C-3, and the isomerization of the C-5 double bond to C-4. The synthesis takes place in the zona fasciculata of the cortex of the adrenal glands. While the

adrenal cortex produces aldosterone (in the zona glomerulosa) and some sex hormones (in the zona reticulosa), cortisol is its main secretion. (The name cortisol comes from cortex.) The medulla of the adrenal gland lies under the cortex and mainly secretes epinephrine and norepinephrine under sympathetic stimulation.

The synthesis of cortisol in the adrenal gland is stimulated by the anterior lobe of the pituitary gland with adrenocorticotropic hormone (ACTH); production of ACTH is in turn stimulated by corticotropin-releasing hormone (CRH), released by the hypothalamus.

Physiology

The amount of cortisol present in the serum undergoes diurnal variation, with the highest levels present in the early morning, and lower levels in the evening, several hours after the onset of sleep. Information about the light/dark cycle is transmitted from the retina to the paired suprachiasmatic nuclei in the hypothalamus. Changed patterns of serum cortisol levels have been observed in connection with abnormal ACTH levels, clinical depression, psychological stress, and such physiological stressors as hypoglycemia, illness, fever, trauma, surgery, fear, pain, physical exertion or extremes of temperature. There is also significant individual variation, although a given person tends to have consistent rhythms.

Cortisol also inhibits the secretion of corticotropin releasing hormone (CRH), resulting in feedback inhibition of ACTH secretion. Some researchers believe that this normal feedback system may break down when animals are exposed to chronic stress.

In normal release, cortisol has widespread actions which help restore homeostasis after stress. It acts as a physiological antagonist to insulin by promoting gluconeogenesis, breakdown of lipids, and proteins, and mobilization of extrahepatic amino acids and ketone bodies. This leads to increased blood glucose concentrations, resulting in increased glycogen formation in the liver (Freeman, 2002). It also increases blood pressure. The hormone lowers the activity of the immune system in the blood. It reflects leukocyte redistribution to lymph nodes, bone marrow, and skin (Cohen, 1972; Cox & Ford, 1982; Dhabhar & McEwen, 1996; Dhabhar and Dhabhar; Fauci, 1975; Fauci & Dale, 1974; Fauci & Dale, 1975; Yu et al., 1974). Acute administration of corticosterone (the endogenous Type I and Type II receptor agonist), or RU28362 (a specific Type II receptor agonist), to adrenalectomized animals induced changes in leukocyte distribution. Bone formation is also lowered by cortisol.

These normal endogenous functions are the basis for the physiological consequences of chronic stress - prolonged cortisol secretion causes muscle wastage, hyperglycemia, and suppresses immune / inflammatory responses. The same consequences arise from long-term use of glucocorticoid drugs.

Also, long-term exposure to cortisol results in damage to cells in the hippocampus. This damage results in impaired learning. However, short-term exposure of cortisol helps to create memories; this is the proposed mechanism for storage of flash bulb memories.

Most serum cortisol, all but about 4%, is bound to proteins including corticosteroid binding globulin (*CBG*), and albumin. Only free cortisol is available to most receptors.

THE DISORDERS OF CORTISOL SECRETION

	Plasma Cortisol	Plasma ACTH
Primary Hypercortisolism	↑	↓
Secondary Hypercortisolism (pituitary, Cushing Disease)	↑	↑
Primary Hypocortisolism (Addison Disease)	↓	↑
Secondary Hypocortisolism (pituitary)	↓	↓

Pharmacology

As an oral or injectable drug, cortisol is also known as hydrocortisone. It is used as an immunosuppressive drug, given by injection in the treatment of severe allergic reactions such as anaphylaxis and angioedema, in place of prednisolone in patients who need steroid treatment but cannot take oral medication, and peri-operatively in patients on long-term steroid treatment to prevent an Addisonian crisis.

It is given by topical application for its anti-inflammatory effect in allergic rashes, eczema and certain other inflammatory conditions. Brand names include Emocort®, Epifoam®, Sigmacort®, Hyderm®, NovoHydrocort® Cortoderm®, Cortizone-10®, Cortaid®, and Lanacort®

It may also be injected into inflamed joints resulting from diseases such as gout.

Compared to prednisolone, hydrocortisone is about 1/4th the strength. Dexamethasone is about 40 times stronger than hydrocortisone. For side effects, see corticosteroid and prednisolone.

Diseases

- *Hypercortisolism*: Excessive levels of cortisol in the blood result in Cushing's syndrome.
- *Hypocortisolism, or adrenal insufficiency*: If on the other hand the adrenal glands do not produce sufficient amounts of cortisol, Addison's disease is the consequence.

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Antianginals

An *antianginal* is any drug used in the treatment of angina pectoris, a symptom of ischaemic heart disease.

Drugs used are nitrates such as nitroglycerin (glyceryl trinitrate) or pentaerythritol tetranitrate; beta blockers, either cardioselectives such as acebutolol or metoprolol, or non-cardioselectives such as oxprenolol or sotalol; or calcium channel blockers, either Class I agents (e.g., verapamil), Class II agents (e.g., amlodipine, nifedipine), or the Class III agent diltiazem.

Nitrates cause vasodilation of the venous capacitance vessels by simulating the endothelium-derived relaxing factor (EDRF). Used to relieve both exertional and vasospastic angina by allowing venous pooling, reducing the pressure in the ventricles and so reducing wall tension and oxygen requirements in the heart. Short-acting nitrates are used to abort angina attacks that have occurred, while longer-acting nitrates are used in the prophylactic management of the condition.

Beta blockers are used in the prophylaxis of exertional angina by reducing the work the heart is allowed to perform below the level that would provoke an angina attack. They cannot be used in vasospastic angina and can precipitate heart failure.

Calcium ion (Ca**++**) antagonists (Calcium channel blockers) are used in the treatment of both exertional and vasospastic angina. In vitro, they dilate the coronary and peripheral arteries and have negative inotropic and chronotropic effects - decreasing afterload, improving myocardial efficiency, reducing heart rate and improving coronary blood flow. In vivo, the vasodilation and hypotension trigger the baroreceptor reflex. Therefore the net effect is the interplay of direct and reflex actions. Class I antiarrhythmic agents have the most potent negative inotropic effect and may cause heart failure; Class II agents do not depress conduction or contractility; the Class III agent has negligible inotropic effect and causes almost no reflex tachycardia.

Beta blockers

Beta blockers (sometimes written as ^{2}*-blockers*) are a class of drugs used for various indications, but particularly for the management of cardiac arrhythmias and cardioprotection after myocardial infarction. Whilst once first-line treatment for hypertension, their role was downgraded in June 2006 in the United Kingdom to fourth-line as they perform less well than other drugs, particularly in the elderly, and there is increasing evidence that the most frequently used beta-blockers at usual doses carry an unacceptable risk of provoking type 2 diabetes.[1]

Beta blockers may also be referred to as *beta-adrenergic blocking agents*, *beta-adrenergic antagonists*, or *beta antagonists*.

Pharmacology

Beta blockers block the action of endogenous catecholamines,

There are three known types of beta receptor, designated ^{2}***1***, ^{2}***2*** and ^{2}***3***. ^{2}***1***-Adrenergic receptors are located mainly in the heart, kidney, and adipose tissue. ^{2}***2***-Adrenergic receptors are located mainly in the heart, lung, GI tract, liver, pancreas, and skeletal muscle. The role and location of ^{2}***3***-receptors is less well-defined.

2-Receptor antagonism

Stimulation of ^{2}***1*** receptors by epinephrine induces a positive chronotropic and inotropic effect on the heart and increases cardiac conduction velocity and automaticity. Stimulation of ^{2}2 receptors induces smooth muscle relaxation (resulting in vasodilation and bronchodilation amongst other actions), induces tremor in skeletal muscle, increases glycogenolysis in the liver and skeletal muscle.

Beta blockers inhibit these normal epinephrine-mediated sympathetic actions, but have minimal effect on resting subjects. That is, they reduce the effect of excitement/physical exertion on heart rate and force of contraction, dilation of blood vessels, opening of bronchi, reduce tremor, and breakdown of glycogen.

It is therefore somewhat unexpected that non-selective beta blockers have an antihypertensive effect, since they appear to cause vasoconstriction. The antihypertensive mechanism appears to involve: reduction in cardiac output (due to negative chronotropic and inotropic effects), reduction in renin release from the kidneys, and a central nervous system effect to reduce sympathetic activity.

Antianginal effects result from negative chronotropic and inotropic effects, which decrease cardiac workload and oxygen demand.

The antiarrhythmic effects of beta blockers arise from sympathetic nervous system blockade – resulting in depression of sinus node function and atrioventricular node conduction, and prolonged atrial refractory periods. Sotalol, in particular, has additional antiarrhythmic properties and prolongs action potential duration through potassium channel blockade.

Intrinsic sympathomimetic activity

Some beta blockers (e.g. oxprenolol and pindolol) exhibit intrinsic sympathomimetic activity (ISA). These agents are capable of exerting low level agonist activity at the ^{2}-adrenergic receptor while simultaneously acting as a receptor site antagonist. These agents, therefore, may be useful in individuals exhibiting excessive bradycardia with sustained beta blocker therapy.

Agents with ISA are not used post-myocardial infarction as they have not been demonstrated to be beneficial. They may also be less effective than other beta blockers in the management of angina and tachyarrhythmia (Rossi, 2006).

+-1-Receptor antagonism

Some beta blockers (e.g. labetalol and carvedilol) exhibit mixed antagonism of both ²- and ±***1***-adrenergic receptors, which provides additional arteriolar vasodilating action.

Other effects

Beta blockers decrease nocturnal melatonin release, perhaps partly accounting for sleep disturbance caused by some agents (Stoschitzky et al., 1999).

Clinical use

Large differences exist in the pharmacology of agents within the class, thus not all beta blockers are used for all indications listed below.

Indications for beta blockers include:

- Hypertension
- Angina
- Cardiac arrhythmia
- Congestive heart failure
- Myocardial infarction
- Glaucoma
- Migraine prophylaxis
- Symptomatic control (tachycardia, tremor) in anxiety and hyperthyroidism
- Essential tremor
- Phaeochromocytoma, in conjunction with ±-blocker

Beta blockers have also been used in the following conditions:

- Hypertrophic obstructive cardiomyopathy
- Acute dissecting aortic aneurysm
- Marfan syndrome (chronic treatment with propranolol slows progression of aortic dilation and its complications)
- Prevention of variceal bleeding in portal hypertension
- Possible mitigation of hyperhidrosis

Congestive heart failure

Although beta blockers were once contraindicated in congestive heart failure, as they have the potential to worsen the condition, studies in the late 1990s showed their positive effects on morbidity and mortality in congestive heart failure (Hjalmarson, 2000; Leizorovicz, 2002; Packer, 2002). Bisoprolol, carvedilol and sustained-release metoprolol are specifically indicated as adjuncts to standard ACE inhibitor and diuretic therapy in congestive heart failure.

Anxiety and performance enhancement

Some people, particularly musicians, use beta blockers to avoid stage fright and tremor during public performance and auditions. The physiological symptoms of the fight/flight response associated with performance anxiety and panic (pounding heart, cold/clammy hands, increased respiration, sweating, etc.) are significantly reduced, thus enabling anxious individuals to concentrate on the task at hand.

Currently, no beta blocker is approved for anxiolytic use by the US FDA. Still, use of beta blockers to combat the physical symptoms of anxiety is not uncommon, particularly among performers, and there are studies which confirm their efficacy as an anxiolytics. (Schneier 2006)

Since they lower heart rate and reduce tremor, beta blockers have been used by some Olympic marksmen to enhance performance, though beta blockers are banned by the International Olympic Committee (IOC).

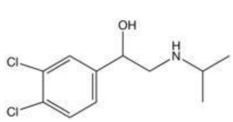
Adverse effects

Common adverse drug reactions (ADRs) associated with the use of beta blockers include: nausea, diarrhoea, bronchospasm, dyspnoea, cold extremities, exacerbation of Raynaud's syndrome, bradycardia, hypotension, heart failure, heart block, fatigue, dizziness, abnormal vision, decreased concentration, hallucinations, insomnia, nightmares, depression, sexual dysfunction, erectile dysfunction and/or alteration of glucose and lipid metabolism. Mixed ±1/^{2}-antagonist therapy is also commonly associated with orthostatic hypotension. Carvedilol therapy is commonly associated with oedema. (Rossi, 2006)

Central nervous system (CNS) adverse effects (hallucinations, insomnia, nightmares, depression) are more common in agents with greater lipid solubility, which are able to cross the blood-brain barrier into the CNS. Similarly, CNS adverse effects are less common in agents with greater aqueous solubility (listed below).

Adverse effects associated with ^{2}***2***-adrenergic receptor antagonist activity (bronchospasm, peripheral vasoconstriction, alteration of glucose and lipid metabolism) are less common with ^{2}***1***-selective (often termed "cardioselective") agents, however receptor selectivity diminishes at higher doses.

Examples of beta blockers


Dichloroisoprenaline, the first beta blocker.

Historical

- Dichloroisoprenaline

Practolol
Pronethaolol

Non-selective agents

- Alprenolol
Carteolol
Levobunolol
Mepindolol
Metipranolol
Nadolol
Oxprenolol
Penbutolol
Pindolol
Propranolol
Sotalol
Timolol

21-Selective agents

- Acebutolol
Atenolol
Betaxolol
Bisoprolol
Esmolol
Metoprolol
Nebivolol

Mixed +-1/2-adrenergic antagonists

- Carvedilol
Celiprolol
Labetalol

22-Selective agents

- Butoxamine (weak ±-adrenergic agonist activity)

Comparative information

Pharmacological differences

- Agents with intrinsic sympathomimetic action (ISA)
  - Acebutolol, carteolol, celiprolol, mepindolol, oxprenolol, pindolol
- Agents with greater aqueous solubility
  - Atenolol, celiprolol, nadolol, sotalol

- Agents with membrane stabilising activity
  - Acebutolol, betaxolol, pindolol, propranolol
- Agents with antioxidant effect
  - Carvedilol

Indication differences

- Agents specifically indicated for cardiac arrhythmia
  - Esmolol, sotalol
- Agents specifically indicated for congestive heart failure
  - Bisoprolol, carvedilol, sustained-release metoprolol
- Agents specifically indicated for glaucoma
  - Betaxolol, carteolol, levobunolol, metipranolol, timolol
- Agents specifically indicated for myocardial infarction
  - Atenolol, metoprolol, propranolol
- Agents specifically indicated for migraine prophylaxis
  - Timolol, propranolol

Propranolol is the only agent indicated for control of tremor, portal hypertension and oesophageal variceal bleeding, and used in conjunction with ±-blocker therapy in phaeochromocytoma (Rossi, 2006).

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Footnotes

1. ^ Sheetal Ladva (28/06/2006). NICE and BHS launch updated hypertension guideline. National Institute for Health and Clinical Excellence. Retrieved on 2006-09-30.

Calcium channel blockers

Calcium channel blockers are a class of drugs with effects on many excitable cells of the body, like the muscle of the heart, smooth muscles of the vessels or neuron cells. The latter are used as antiepileptics and are not covered in this article.

The main action of calcium channel blockers is to lower the blood pressure. It is for this action that it is used in individuals with hypertension.

Most calcium channel blockers decrease the force of contraction of the myocardium (muscle of the heart). This is known as the negative inotropic effect of calcium channel blockers. It is because of the negative inotropic effects of most calcium channel blockers that they are avoided (or used with caution) in individuals with cardiomyopathy

Many calcium channel blockers also slow down the conduction of electrical activity within the heart, by blocking the calcium channel during the plateau phase of the action potential of the heart (see: cardiac action potential). This causes a lowering of the heart rate and may cause heart blocks. This is known as the negative chronotropic effect of calcium channel blockers. The negative chronotropic effects of calcium channel blockers make them a commonly used class of agents in individuals with atrial fibrillation or flutter in whom control of the heart rate is an issue.

Mechanism of action

Calcium channel blockers work by blocking voltage-sensitive calcium channels in the heart and in the blood vessels. This prevents calcium levels from increasing as much in the cells when stimulated, leading to less contraction.

This decreases total peripheral resistance by dilating the blood vessels, and decreases cardiac output by lowering the force of contraction. Because resistance and output drop, so does blood pressure.

With low blood pressure, the heart does not have to work as hard; this can ease problems with cardiomyopathy and coronary disease.

Unlike with beta-blockers, the heart is still responsive to sympathetic nervous system stimulation, so blood pressure can be maintained more effectively.

List of calcium channel blockers

Dihydropyridine calcium channel blockers

- Amlodipine **(Norvasc)**
- Felodipine (Plendil)
Nicardipine (Cardene, Carden SR)
Nifedipine (Procardia, Adalat)
Nimodipine (Nimotop)
Nisoldipine (Sular)
Nitrendipine (Cardif, Nitrepin)
Lacidipine (Motens)
Lercanidipine (Zanidip)

Phenylalkylamine calcium channel blockers

- Verapamil (Calan, Isoptin)
Gallopamil (D600)

Benzothiazepine calcium channel blockers

- Diltiazem (Cardizem)

Other

- Menthol (mint oil)

Other drugs with similar uses

Other classes of pharmaceutical agents that have overlapping effects as calcium channel blockers include ACE inhibitors, beta-blockers, and nitrates.

Amlodipine (Norvasc)

***Amlodipine* Systematic (IUPAC) name**

3-ethyl-5-methyl-2-(2-aminoethoxymethyl)-4-(2- chlorophenyl)-1,4-dihydro-6-methyl-3,5-pyridinedicarboxylate benzenesulfonate

Identifiers

CAS number 88150-42-9

ATC code **C08**CA01

PubChem 2162

DrugBank APRD00520

Chemical data

Formula $C_{20}H_{25}ClN_2O_5.C_6H_6O_3S$

Mol. weight 408.879 g/mol

Pharmacokinetic data

Bioavailability 64 to 90%

Metabolism Hepatic

Half life 30 to 50 hours

Excretion Renal

Therapeutic considerations

Pregnancy cat. $C_{(AU)}$ $C_{(US)}$

Legal status $POM_{(UK)}$ $_{-only(US)}$

Routes Oral (tablets)

Amlodipine (as besylate, mesylate or maleate) is a long-acting calcium channel blocker used as an anti-hypertensive and in the treatment of angina. Amlodipine is marketed as *Norvasc*® in North America and as *Istin*® in the United Kingdom as well as under various other names. As other calcium channel blockers, amlodipine acts by relaxing the smooth muscle in the arterial wall, decreasing peripheral resistance and hence improving blood pressure; in angina it improves blood flow to the myocardium. It was developed under the direction of Dr. Simon Campbell.

Indications

- hypertension
prophylaxis of angina

Cautions

- hepatic impairment
pregnancy

Contra-indications

- cardiogenic shock
unstable angina
significant aortic stenosis
breast feeding

Side effects

Some side effects of the use of amlodipine may be:

- Very often: peripheral edema (feet and ankles) - in 1 of 10 users
Often: dizziness, palpitations, muscle, stomach or headache, dyspepsia, nausea - in 1 in 100 users
Sometimes: blood disorders, development of breasts in men (gynecomastia), impotence, depression, insomnia, tachycardia - in 1 in 1,000 users
Rarely: erratic behavior, hepatitis, jaundice - in 1 in 10,000 users
Very rarely: hyperglycemia, tremor, Stevens-Johnson syndrome - in 1 in 100,000 users

Source: Sandoz product information sheet

Dose

- Hypertension or angina: 5 or 10 mg once daily.

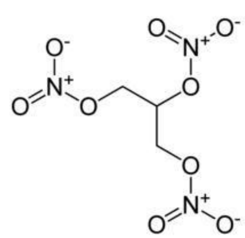
Salts

In the United Kingdom tablets of amlodipine from different suppliers may contain different salts. The strength of the tablets is expressed in terms of amlodipine base. i.e. without the salt. Tablets containing different salts are therefore considered interchangeable.

Patent Loss

Pfizer patent protection on Norvasc until 2007.

Nitroglycerin



Propane-1,2,3-triyl trinitrate
IUPAC name

Chemical formula $C_3H_5N_3O_9$

Molecular mass 227.0872 g/mol

Shock sensitivity Very high

Friction sensitivity Very high

Density 1.13 kg/dm^3 at 15 °C

Explosive velocity 7700 m/s

RE factor 1.50

Melting point 13.2 °C (55.76 °F)

Autoignition temperature Decomposes at 50 to 60 °C (122 to 140 °F)

Appearance Clear yellow/colorless oily liquid

CAS number 55-63-0

PubChem 4510

SMILES
C(C(CO[N+](=O)[O-])O
[N+](=O)[O-])O[N+](=O)[O-]

Nitroglycerin, also known as *nitroglycerine*, *trinitroglycerin*, and *glyceryl trinitrate*, is a chemical compound. It is a heavy, colorless, addictive, oily, explosive liquid obtained by nitrating glycerol. It is used in the manufacture of explosives, specifically dynamite, and as such is employed in the construction and demolition industries. It is also used medically as a vasodilator to treat heart conditions.

History

Nitroglycerin was discovered by chemist Ascanio Sobrero in 1847, working under TJ Pelouze at the University of Torino. The best manufacturing process was developed by Alfred Nobel in the 1860s. His company exported a liquid combination of nitroglycerin and gunpowder as 'Swedish Blasting Oil', but the extreme danger as a result of its extreme

instability, as shown in a number of "appalling catastrophes," led to the liquid being widely banned and to the development of dynamite (and similar mixtures such as dualine and lithofracteur), mixing the nitroglycerine with inert (Nobel used kieselguhr) or combustible absorbents (e.g., nitrocellulose to produce the yellow gel, blasting gelatine).

Instability and desensitization

In its pure form, it is a contact explosive (i.e., physical shock can cause it to explode) and degrades over time to even more unstable forms. This makes it highly dangerous to transport or use. In this undiluted form it is one of the most powerful high explosives, comparable to the military explosives RDX and PETN (which are not used in munitions at full concentration because of their sensitivity) as well as the plastic explosive C-4.

Early in the history of this explosive it was discovered that liquid nitroglycerin can be "desensitized" by cooling to 5 to 10 °C (40 to 50 °F), at which temperature it freezes, contracting upon solidification. However, later thawing can be extremely sensitizing, especially if impurities are present or if warming is too rapid. It is possible to chemically "desensitize" nitroglycerin to a point where it can be considered approximately as "safe" as modern High Explosive formulations, by the addition of approximately 10 to 30% ethanol, acetone, or dinitrotoluene (percentage varies with the desensitizing agent used). Desensitization requires extra effort to reconstitute the "pure" product. Failing this, it must be assumed that desensitized nitroglycerin is substantially more difficult to detonate, possibly rendering it useless as an explosive for practical application.

A serious problem in the use of nitroglycerin results from its high freezing point (13 °C [55 °F]). Solid nitroglycerin is much less sensitive to shock than the liquid, a feature common in explosives and in the past it has often been shipped in the frozen state, but this has resulted in a high number of accidents during the thawing process by the end user just prior to use. This disadvantage is overcome by using mixtures of nitroglycerin with other polynitrates; for example, a mixture of nitroglycerin and ethylene glycol dinitrate freezes at -29 °C (-20 °F).[1]

Detonation

Nitroglycerin and any or all of the diluents mentioned above can certainly deflagrate or burn. However, the explosive power of nitroglycerin is derived from detonation: energy from the initial decomposition causes a pressure gradient which detonates the surrounding fuel. This can generate a self-sustained shock-wave that propagates through the fuel-rich medium at or above the speed of sound as a cascade of near-instantaneous pressure-induced decomposition of the fuel into gas. This is quite unlike deflagration, which depends solely upon available fuel, regardless of pressure or shock.

Preparation

Nitroglycerin is prepared by nitration of glycerol (also known as glycerin). In the process, glycerin is slowly tipped into a mix of full concentration nitric and sulfuric acids (about 50% sulfuric acid, 40% nitric acid, and 5-10% glycerin). The mixed acid must be cooled to

approximately room temperature before the glycerin is added because they exotherm (heat up) greatly when combined. The solution is slowly stirred. A few seconds after mixing, the vessel must be immersed in a jacket of ice water to prevent the exothermic reaction from overheating it, causing nitric acid decomposition or even explosion. The temperature should never exceed 30 °C (86 °F), but the chemicals must not be cooled by the ice water before mixing, or the nitrating reaction will not take place.

If the reaction is successful, the nitroglycerin will form a slightly yellow or straw colored liquid which will float to the top of the acid mix. The mix is then carefully poured into a large container of water. The nitroglycerin will settle to the bottom (it is water insoluble) and should be neutralized with sodium carbonate and water mix until its pH becomes neutral.

Manufacturing

The industrial manufacturing process often uses a nearly 50:50 mixture of sulfuric acid and nitric acid. This can be produced by mixing white fuming nitric acid (quite costly pure nitric acid in which oxides of nitrogen have been removed, as apart from red fuming nitric acid) and concentrated sulfuric acid. More often, this mixture is attained by the cheaper method of mixing fuming sulfuric acid (sulfuric acid containing excess sulfur trioxide) and azeotropic nitric acid (consisting of around 70% nitric acid, the rest being water).

The sulfuric acid produces protonated nitric acid species, which are attacked by glycerin's nucleophilic oxygen atoms. The nitro group is thus added as an ester C-O-NO2 and water is produced. This is apart from an aromatic nitration reaction in which nitronium ions are the active species in an electrophilic attack of the molecules ring system.

The addition of glycerin results in an exothermic reaction (i.e., heat is produced), as usual for mixed acid nitrations. However, if the mixture becomes too hot, it results in runaway, a state of accelerated nitration accompanied by the destructive oxidizing of organic materials of nitric acid and the release of very poisonous brown nitrogen dioxide gas at high risk of an explosion. Thus, the glycerin mixture is added slowly to the reaction vessel containing the mixed acid (not acid to glycerin as one might expect). The nitrator is cooled with cold water or some other coolant mixture and maintained throughout the glycerin addition at about 22 °C, much below which the esterification occurs too slowly to be useful. The nitrator vessel, often constructed of iron or lead and generally stirred with compressed air, has an emergency trap door at its base, which hangs over a large pool of very cold water and into which the whole reaction mixture (called the charge) can be dumped to prevent an explosion, a process referred to as drowning. If the temperature of the charge exceeds about 30 °C (actual value varying by country) or brown fumes are seen in the nitrators vent, then it is immediately drowned.

Due to the great dangers associated with its production, most nitroglycerin production facilities are in offshore rigs or very remote locations.

Medical use

In medicine, nitroglycerin (sometimes called Glyceryl trinitrate, presumably to avoid alarming people) is used as a heart medication (under the trade names *Nitrospan®* and

Nitrostat®). It is used as a medicine for angina pectoris (ischaemic heart disease) in tablets, ointment, solution for intravenous use, transdermal patches (*Transderm Nitro*®, *Nitro-Dur*®), or sprays administered under the tongue (*Nitrolingual Pump Spray*®, *Natispray*®). A recent medical development will include a small amount of nitroglycerin in the tip of a new Durex condom to stimulate erection during intercourse. "The CSD500 condom contains a chemical in its teat, called glyceryl trinitrate (GTN), which is absorbed by the skin and causes blood vessels to dilate." According to anecdotal evidence, Nitroglycerin patches have also found use as treatment for the bite of the Brown recluse spider, which has a vasoconstricting venom. However, research has suggested that Nitroglycerin has negligible benefits and might even increased inflammation of the bite wound.

The principal action of nitroglycerin is vasodilation -- that is, widening of the blood vessels. The main effects of nitroglycerin in episodes of angina pectoris are

- subsiding of chest pain
- decrease of blood pressure
- increase of heart rate.

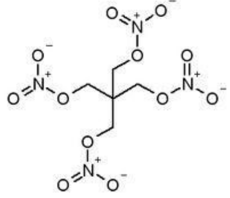
These effects arise because nitroglycerin is converted to nitric oxide in the body (by a mechanism that is not completely understood), and nitric oxide is a natural vasodilator. Recently, it has also become popular in an off-label use at reduced (0.2%) concentration in ointment form as an effective treatment for anal fissure.

Humans develop a tolerance and addiction to nitroglycerin after long-term exposure. Withdrawal symptoms include headaches, heart problems, and even death; with re-exposure to nitroglycerin these symptoms may disappear. For workers in nitroglycerin manufacturing facilities, this can result in a "Monday Morning Headache" phenomena for those who experience regular nitroglycerin exposure in the workplace; over the weekend they develop symptoms of withdrawal, which are then countered by reexposure on the next work day.

See also

- Uncle Fester. Author of Home Workshop Explosives which goes in detail of how the underground chemist can easily manufacture his own explosives.

PETN



PETN

1,3-Dinitrato-2,2-bis (nitratomethyl)propane
IUPAC name

Chemical formula C5H8N4O12

Molecular mass 316.14 g/mol

Shock sensitivity Medium

Friction sensitivity Medium

Density 1.773 kg/m^3 at 20 °C

Explosive velocity 8,400 m/s

RE factor 1.66

Melting point 141.3 °C

Autoignition temperature Decomposes at 190 °C

Appearance Odourless white, crystalline solid.

CAS number 78-11-5

PETN (Pentaerythritol Tetranitrate, also known as Penthrite) is one of the strongest known high explosives, with a relative effectiveness factor (R.E. factor) of 1.66. It is more sensitive to shock or friction than TNT or tetryl, and it is never used alone as a booster. It is primarily used in booster and bursting charges of small caliber ammunition, in upper charges of detonators in some land mines and shells, and as the explosive core of detonation cord.

PETN is one of the explosive ingredients used in Semtex plastic explosive. During World War II the M9A1 2.36" Rocket Launcher (Bazooka) shaped charge, with 8 oz of pentolite (a mixture of PETN and TNT), could penetrate up to 5 inches of armor.

Demolition charge, M118, commonly called Flex-X or sheet explosive, consists of 4 half-pound sheets of flexible explosive packed in a plastic envelope. Each sheet is approximately 3 inches wide, 12 inches long, and ¼ inch thick. Note: The exact explosive contained in an M118 charge varies with the manufacturer. At present, some manufacturers use PETN as the basic explosive. Others use RDX. Charges manufactured in the future may include other explosives.

PETN is also used as a vasodilator. The medicine for heart diseases, "Lentonitrat", is pure PETN.

PETN was also used by Richard Reid for the plot to destroy American Airlines Flight 63 by trying to ignite explosives hidden in his shoes.

Properties

The velocity of detonation of PETN at a density of 1.7 is 8,400 meters per second.

PETN's formula is $C(CH_2ONO_2)_4$. Its theoretical maximum crystal density is 1.773 g/cm^3. It melts toward 141 °C.

As a pollutant in the environment

PETN does not occur naturally, so the production and use of this kind of compound can lead to contamination of the environment. PETN is subject to biodegradation in untreated or unpreserved urine and feces. There also have been some reports of its degradation by bacteria, whose PETN reductase denitrates PETN into trinitrates and then dinitrates (French et al., 1996). The last compound shown in the pathway, pentaerythritol dinitrate, is degraded further to unknown products.

Production

PETNs' preparation involves the nitration of pentaerythritol with a mixture of concentrated nitric and sulfuric acid. The preferred method of nitration is the ICI method, which utilizes concentrated nitric acid (98%+) alone, as mixed acid can create unstable sulfonated by-products.

$C(CH_2OH)_4 + 4HNO_3$ ’ $C(CH_2ONO_2)_4 + 4H_2O$

References

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Antiarrhythmic agents

Antiarrhythmic agents are a group of pharmaceuticals that are used to suppress fast rhythms of the heart (cardiac arrhythmias), such as atrial fibrillation, atrial flutter, ventricular tachycardia, and ventricular fibrillation.

While the use of antiarrhythmic agents to suppress atrial arrhythmias (atrial fibrillation and atrial flutter) is still in practice, it is unclear whether suppression of atrial arrhythmias will prolong life [1][2].

In the past, it was believed that suppression of the potentially dangerous ventricular arrhythmias, ventricular tachycardia and ventricular fibrillation would prolong life, but it was found in large clinical trials that suppression of these arrhythmias would paradoxically increase mortality[3][4], which may happen due to the increased workload these drugs place on the heart.

In individuals with atrial fibrillation, antiarrhythmics are still used to suppress arrhythmias. This is often done to relieve the symptoms that may be associated with the loss of the atrial component to ventricular filling (atrial kick) that is due to atrial fibrillation or flutter.

In individuals with ventricular arrhythmias, antiarrhythmic agents are often still in use to suppress arrhythmias. In this case, the patient may have frequent arrhythmic events or be at high risk for ventricular arrhythmias. Antiarrhythmic agents may be considered the first-line therapy in the prevention of sudden death in certain forms of structural heart disease, and failure of these agents to suppress arrhythmias may lead to implantation of an implantable cardioverter-defibrillator (ICD).

The use of antiarrhythmic agents in this population may be in conjunction with an ICD. In this case, the ICD is used to prevent sudden death due to ventricular fibrillation, while the antiarrhythmic agent(s) are used to suppress ventricular tachyarrhythmias so that the ICD doesn't shock the patient frequently.

Many attempts have been made to classify antiarrhythmic agents. The problem arises from the fact that many of the antiarrhythmic agents have multiple modes of action, making any classification imprecise.

Vaughan Williams antiarrhythmic classification

The Vaughan Williams classification is one of the most widely used classification schemes for antiarrhythmic agents. This scheme classifies a drug based on the primary mechanism of its antiarrhythmic effect. However, its dependence on primary mechanism is one of the limitations of the VW classification, since many antiarrhythmic agents have multiple action mechanisms. Amiodarone, for example, has effects consistent with all of the first four classes. Another limitation is the lack of consideration within the VW classification system for the effects of drug metabolites. Procainamide—a class Ia agent whose metabolite N-acetyl procainamide (NAPA) has a class III action—is one such example. A historical limitation was that drugs such as digoxin and adenosine – important antiarrhythmic agents – had no place at all in the VW classification system. This has since been rectified by the inclusion of class V.

There are five main classes in the Vaughan Williams classification of antiarrhythmic agents:

- Class I agents interfere with the sodium (Na+) channel.
- Class II agents are anti-sympathetic nervous system agents. All agents in this class are beta blockers.
- Class III agents affect potassium (K+) efflux.
- Class IV agents affect the AV node.
- Class V agents work by other or unknown mechanisms.

Class I agents

The class I antiarrhythmic agents interfere with the sodium (Na+) channel. Class I agents are grouped by what effect they have on the Na+ channel, and what effect they have on cardiac action potentials.

Class Ia agents

Class Ia agents block the fast sodium channel. Blocking this channel depresses the phase 0 depolarization (reduces V***max***), which prolongs the action potential duration by slowing conduction. Agents in this class also cause decreased conductivity and increased refractoriness.

Indications for Class Ia agents are supraventricular tachycardia, ventricular tachycardia, symptomatic ventricular premature beats, and prevention of ventricular fibrillation.

Procainamide can be used in the treatment of atrial fibrillation in the setting of Wolff-Parkinson-White syndrome, and in the treatment of wide complex hemodynamically stable tachycardias.

While procainamide and quinidine may be used in the conversion of atrial fibrillation to normal sinus rhythm, they should only be used in conjunction with an AV node blocking agent (ie: digoxin, verapamil, or a beta blocker), because procainamide and quinidine can increase the conduction through the AV node and may cause 1:1 conduction of atrial fibrillation, causing an increase in the ventricular rate.

Class Ia agents include quinidine, procainamide and disopyramide.

Class Ib agents

Class Ib antiarrhythmic agents are sodium channel blockers. Class Ib agents have fast onset and offset kinetics, meaning that they have little or no effect at slower heart rates, and more effects at faster heart rates. Class Ib agents shorten the action potential duration and reduce refractoriness. These agents will decrease V***max*** in partially depolarized cells with fast response action potentials. They either do not change the action potential duration, or they may decrease the action potential duration.

Class Ib agents are indicated for the treatment of ventricular tachycardia and symptomatic premature ventricular beats, and prevention of ventricular fibrillation.

Class Ib agents include lidocaine, mexiletine, tocainide, and phenytoin.

Class Ic agents

Class Ic antiarrhythmic agents markedly depress the phase 0 depolarization (decreasing V***max***). They decrease conductivity, but have a minimal effect on the action potential duration. Of the sodium channel blocking antiarrhythmic agents (the class I antiarrhythmic agents), the class Ic agents have the most potent sodium channel blocking effects.

Class Ic agents are indicated for life-threatening ventricular tachycardia or ventricular fibrillation, and for the treatment of refractory supraventricular tachycardia (ie: atrial fibrillation).It can be toxic and can affect the reproductive system.

Class Ic agents include encainide, flecainide, moricizine, and propafenone.

Class II agents

Class II agents are conventional beta blockers. They act by selectively blocking the effects of catecholamines at the ^{2}1-adrenergic receptors, thereby decreasing sympathetic activity on the heart. These agents are particularly useful in the treatment of supraventricular tachycardias. They decrease conduction through the AV node.

Class II agents include esmolol, propranolol, and metoprolol.

Class III agents

Class III agents predominantly block the potassium channels, thereby prolonging repolarization[5]. Since these agents do not affect the sodium channel, conduction velocity is not decreased. The prolongation of the action potential duration and refractory period, combined with the maintenance of normal conduction velocity, prevent re-entrant arrhythmias. (The re-entrant rhythm is more like to interact with tissue that has become refractory).

Class III antiarrhythmic agents exhibit reverse use dependent prolongation of the action potential duration (*Reverse use-dependence*). This means that the refractoriness of the ventricular myocyte increases at lower heart rates. This increases the susceptibility of the myocardium to early after-depolarizations (EADs) at low heart rates. Antiarrhythmic agents that exhibit reverse use-dependence are more efficacious at preventing a tachyarrhythmia than converting someone into normal sinus rhythm. Because of the reverse use-dependence of class III agents, at low heart rates class III antiarrhythmic agents may paradoxically be more arrhythmogenic.

Amiodarone is indicated for the treatment of refractory VT or VF, particularly in the setting of acute ischemia. Amiodarone is also safe to use in individuals with cardiomyopathy and atrial fibrillation, to maintain normal sinus rhythm.

Sotalol is indicated for the treatment of atrial or ventricular tachyarrhythmias, and AV re-entrant arrhythmias. Ibutilide is the only antiarrhythmic agent currently approved by the Food and Drug Administration for acute conversion of atrial fibrillation to sinus rhythm.

Class III agents include amiodarone, azimilide, bretylium, clofilium, dofetilide, tedisamil, ibutilide, sematilide, and sotalol.

Class IV agents

Class IV agents are slow calcium channel blockers. They decrease conduction through the AV node.

Class IV agents include verapamil and diltiazem.

Class V agents

Class V agents include adenosine and digoxin. Digoxin increases vagal activity via its central action on the central nervous system, thus decreasing the conduction of electrical impulses through the AV node

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Cardiac glycosides

Cardiac glycosides are drugs used in the treatment of congestive heart failure and cardiac arrhythmia. These glycosides are found as secondary metabolites in several plants, but also in some animals. Some of these compounds (ouabain and some frog poisons) are used in Africa as arrow-poisons for hunting.

Cardiac glycosides work by inhibiting the Na^{+}/K^{+} pump. They do this by stabilizing the E2-P transition state of the Na^{+}/K^{+} pump. This inhibition increases the amount of Ca^{++} ions available for contraction of the heart muscle, improves cardiac output and reduces distention of the heart.

They have an antiarrhythmic effect by prolonging the refractory period of the AV node (Atrioventricular node), reducing the number of impulses reaching the ventricles. Cardiac output is restored but atrial fibrillation or atrial flutter are not abolished.

Examples of plants producing cardiac glycosides:

- Strophanthus - ouabain g/k/e-strophanthin
- Digitalis lanata and Digitalis purpurea - digoxin, digitoxin
- Scilla maritima - proscillaridine A
- Adonis vernalis, Adonis aestivalis
- Acokanthera oblongifolia
- Convallaria

Some frog-poison contain bufalin, marinobufagenin and bufadienolides, cardiac glycosides.

Digoxin

Systematic (IUPAC) name

4-[(3S,5R,8R,9S,10S,12R,13S,14S)-3-[(2S,4S,5R,6R)-5-[(2S,4S,5R,6R)-5-[(2S,4S,5R,6R)-4,5-dihydroxy-6-methyl-oxan-2-yl]oxy-4-hydroxy-6-methyl-oxan-2-yl]oxy-4-hydroxy-6-methyl-oxan-2-yl]oxy-12,14-dihydroxy-10,13-dimethyl-1,2,3,4,5,6,7,8,9,11,12,15,16,17-tetradecahydrocyclopenta[a]phenanthren-17-yl]-5H-furan-2-one

Identifiers

CAS number 20830-75-5

ATC code C01**AA02** C01**AA05** C01**AA08**

PubChem 30322

DrugBank APRD00098

Chemical data

Formula $C_{41}H_{64}O_{14}$

Mol. weight 780.938 g/mol

Pharmacokinetic data

Bioavailability 60 to 80% (Oral)

Protein binding 25%

Metabolism Hepatic (16%)

Half life 36 to 48 hours (patients with normal renal function), 3.5 to 5 days (patients with impaired renal function)

Excretion Urinary

Therapeutic considerations

Pregnancy cat. A (Au), C (U.S.)

Legal status S4 (Au), POM (UK), -only (U.S.)

Routes Oral, Intravenous

Digoxin (INN) (IPA: [djÈd'Rksjn]) is a cardiac glycoside extracted from the foxglove plant, digitalis. Its corresponding aglycone is digoxigenin. Digoxin is widely used in the treatment of various heart conditions, namely atrial fibrillation, atrial flutter and congestive heart failure that cannot be controlled by other medication. Digoxin preparations are commonly marketed under the trade name *Lanoxin*.

Actions

The main pharmacological effects of digoxin are on the heart. Extracardiac effects are responsible for many of the adverse effects (see below).

Its main cardiac effects are

- A decrease of conduction of electrical impulses through the AV node, making it a commonly used drug in controlling the heart rate during atrial fibrillation or atrial flutter.
- An increase of force of contraction via inhibition of the Na^{+}/K^{+} ATPase pump (see below).

Mechanism of action

Digoxin binds to a site on the extracellular aspect of the ±-subunit of the Na±/K± ATPase pump in the membranes of heart cells (myocytes). This causes an increase in the level of sodium ions in the myocytes, which then leads to a rise in the level of calcium ions. The proposed mechanism is the following: inhibition of the Na±/K± pump leads to increased Na± levels, which in turn slows down the extrusion of Ca2+ via the Na±/Ca2+ exchange pump. Increased amounts of Ca2+ are then stored in the sarcoplasmic reticulum and released by each action potential, which is unchanged by digoxin. This is a different mechanism from that of catecholamines.

Digoxin also increases vagal activity via its central action on the central nervous system, thus decreasing the conduction of electrical impulses through the AV node. This is important for its clinical use in different arrhythmias (see below).

Clinical use

Today, the most common indications for digoxin are probably atrial fibrillation and atrial flutter with rapid ventricular response. High ventricular rate leads to insufficient diastolic filling time. By slowing down the conduction in the AV node and increasing its refractory period, digoxin can reduce the ventricular rate. The arrhythmia itself is not affected, but the pumping function of the heart improves owing to improved filling.

The use of digoxin in congestive heart failure during sinus rhythm is controversial. In theory the increased force of contraction should lead to improved pumping function of the heart, but its effect on prognosis is disputable and digoxin is no longer the first choice for congestive heart failure. However, it can still be useful in patients who remain symptomatic despite proper diuretic and ACE inhibitor treatment.

Digoxin is usually given by mouth, but can also be given by IV injection in urgent situations (the IV injection should be slow, heart rhythm should be monitored). The half life is about 36 hours, digoxin is given once daily, usually in 125 ¼g or 250 ¼g dosing. In patients with decreased kidney function the half life is considerably longer, calling for a reduction in dosing or a switch to a different glycoside (such as digitoxin which although having a much longer elimination half-life of around 7 days, is mainly eliminated from the body via the liver, and thus not affected by changes in renal function).

Effective plasma levels are fairly well defined, 1-2.6 nmol/l. In suspected toxicity or ineffectiveness, digoxin levels should be monitored. Plasma potassium levels also need to be closely controlled (see side effects below).

Adverse effects

The occurrence of adverse drug reactions is common, owing to its narrow therapeutic index (the margin between effectiveness and toxicity). Adverse effects are concentration-dependent, and are rare when plasma digoxin concentration is <0.8 ¼g/L. [1] They are also more common in patients with low potassium levels (hypokalemia), since digoxin normally competes with K± ions for the same binding site on the Na±/K± ATPase pump.

Common adverse effects (e1% of patients) include: loss of appetite, nausea, vomiting, diarrhoea, blurred vision, visual disturbances (yellow-green halos), confusion, drowsiness, dizziness, nightmares, agitation, and/or depression. Less frequent adverse effects (0.1%–1%) include: acute psychosis, delirium, amnesia, shortened QRS complex, atrial or ventricular extrasystoles, paroxysmal atrial tachycardia with AV block, ventricular tachycardia or fibrillation, heart block [1] but when sytematically sought, the evidence for this is equivocal.[2]

The pharmacological actions of digoxin usually results in electrocardiogram (ECG) changes, including ST depression or T wave inversion, which do not indicate toxicity. PR interval prolongation, however, may be a sign of digoxin toxicity. Additionally, increased intracellular Ca2+ may cause a type of arrhythmia called bigeminy (coupled beats), eventually ventricular tachycardia or fibrillation. The combination of increased (atrial) arrhythmogenesis and inhibited atrio-ventricular conduction (for example paroxysmal atrial tachycardia with A-V block - so-called "PAT with block") is said to be pathognomonic (i.e. diagnostic) of digoxin toxicity.[3]

An often described but rarely seen adverse effect of digoxin is a disturbance of colour vision (mostly yellow and green colour) called xanthopsia.

Digoxin has an interaction with the antimalarial medication Hydroxychloroquine.

Other information

Digoxin has potentially dangerous interaction with verapamil, amiodarone and erythromycin.

In overdose, the usual supportive measures are needed. If arrhythmias prove troublesome, or malignant hyperkalaemia occurs (inexorably rising potassium level due to paralysis of the cell membrane bound ATPase-dependant Na/K pumps), the specific antidote is antidigoxin (antibody fragments against digoxin, trade name Digibind®). [4] Digoxin is not usefully removed by hemodialysis.

Some physical properties of digoxin are water solubility of 64.8 mg/L at 25 °C and melting point at 249.3 °C.

In the news

Charles Cullen admitted in 2003 to killing as many as 40 hospital patients with overdoses of heart medication - usually digoxin - at hospitals in New Jersey and Pennsylvania over his 16-year career as a nurse. On March 10, 2006 he was sentenced to 18 consecutive life sentences and is not eligible for parole for 397 years. [3]

See also

- Cardiac glycoside

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- Lüllmann. Pharmakologie und Toxikologie (15th edition), Georg Thieme Verlag, 2003. ISBN 3-13-368515-5

Adenosine

Adenosine *Systematic (IUPAC) name (2R,3R,4R,5R)-2-(6-aminopurin-9-yl)- 5-(hydroxymethyl)oxolane-3,4-diol*

Identifiers

CAS number 58-61-7

ATC code C01**EB10**

PubChem 60961

DrugBank APRD00132

Chemical data

Formula $C_{10}H_{13}N_5O_4$

Mol. weight 267.242 g/mol

Adenosine is a nucleoside comprised of adenine attached to a ribose (ribofuranose) moiety via a ^{2}-N9-glycosidic bond.

Adenosine plays an important role in biochemical processes, such as energy transfer - as adenosine triphosphate (ATP) and adenosine diphosphate (ADP) - as well as in signal transduction as cyclic adenosine monophosphate, cAMP.

Pharmacological effects

Anti-inflammatory Properties

Adenosine is a potent anti-inflammatory agent, acting at its four G-protein coupled receptors. Topical treatment of adenosine to foot wounds in diabetes mellitus has been shown in lab animals to drastically increase tissue repair and reconstruction. Topical administration of adenosine for use in wound healing deficiencies and diabetes mellitus in humans is currently under clinical investigation.

Action on the heart

When administered intravenously, adenosine causes transient heart block in the AV node. It also causes endothelial dependent relaxation of smooth muscle as is found inside the artery walls. This causes dilatation of the "normal" segments of arteries where the endothelium is not separated from the tunica media by atherosclerotic plaque. This feature allows physicians to use adenosine to test for blockages in the coronary arteries, by exaggerating the difference between the normal and abnormal segments.

In individuals suspected of suffering from a supraventricular tachycardia (SVT), adenosine is used to help identify the rhythm. Certain SVTs can be successfully terminated with adenosine. This includes any re-entrant arrhythmias that require the AV node for the re-entry (e.g., AV reentrant tachycardia (AVRT), AV nodal reentrant tachycardia (AVNRT). In addition, atrial tachycardia can sometimes be terminated with adenosine.

Adenosine has a direct effect on atrial tissue causing a shortening of the refractory period. When administered via a central lumen catheter, adenosine has been shown to initiate atrial fibrillation because of its affect on atrial tissue. In individuals with accessory pathways, the onset of atrial fibrillation can lead to a life threatening ventricular fibrillation.

Fast rhythms of the heart that are confined to the atria (e.g., atrial fibrillation, atrial flutter) or ventricles (e.g., monomorphic ventricular tachycardia) and do not involve the AV node as part of the re-entrant circuit are not typically affected by adenosine.

Because of the effects of adenosine on AV node-dependent SVTs, adenosine is considered a class V antiarrhythmic agent.

The pharmacological effects of adenosine are blunted in individuals who are taking methylxanthines (e.g., caffeine (found in coffee) and theophylline (found predominantly in tea)).

Dosage

When given for the evaluation or treatment of an SVT, the initial dose is 6 mg, given as a fast IV push. Due to adenosine's extremely short half-life, start the IV line as proximal to the

heart as possible, such as the antecubital fossa. If this has no effect (e.g., no evidence of transient AV block), a 12mg dose can be given 1-2 minutes after the first dose. If the 12mg dose has no effect, a second 12mg dose can be administered 1-2 minutes after the previous dose. Some clinicians may prefer to administer a higher dose (typically 18 mg), rather than repeat a dose that apparently had no effect. When given to dilate the arteries, such as in a "stress test", the dosage is typically 0.14 mg/kg/min, administered for 4 or 6 minutes, depending on the protocol.

Consider increasing the recommended dose in patients on theophylline since methylxanthines prevent binding of adenosine at receptor sites. Consider decreasing the dose in patients on dipyridamole (Persantine) and diazepam (Valium) because adenosine potentiates the effects of these drugs.

Consider decreasing the recommended dose in half in patients who are presenting Congestive Heart Failure, Myocardial Infarction, shock, hypoxia, and/or hepatic or renal insufficiency.

Consider decreasing the recommended dose in half for elderly patients.

Drug Interactions

beta blockers and dopamine may precipitate toxicity in the patient.

Contraindications

Poison/Drug induced tachycardia, Asthma (relative contraindication), 2nd or 3rd degree heart block, Atrial fibrillation, atrial flutter, Ventricular tachycardia, Sick sinus syndrome, Stokes-Adams Attack, Wolf-Parkinson-White syndrome, bradycardia with Premature Ventricular Contractions (PVCs).

Side effects

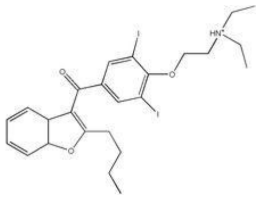
Many individuals experience facial flushing, lightheadedness, diaphoresis, or nausea after administration of adenosine. These symptoms are transitory, usually lasting less than one minute.

Metabolism

When adenosine enters the circulation, it is broken down by adenosine deaminase, which is present in red cells and the vessel wall.

Dipyridamole, an inhibitor of adenosine deaminase, allows adenosine to accumulate in the blood stream. This causes an increase in coronary vasodilatation.

Amiodarone



Amiodarone **Systematic (IUPAC) name**

(2-butylbenzofuran-3-yl)- [4-(2-diethylaminoethoxy)- 3,5-diiodo-phenyl]- methanone (as the hydrochloride salt)

Identifiers

CAS number 1951-25-3

ATC code **C01**BD01

PubChem 2157

DrugBank APRD00288

Chemical data

Formula $C_{25}H_{29}I_2NO_3 \cdot HCl$

Mol. weight 681.78 g/mol

Pharmacokinetic data

Bioavailability 20 - 55%

Metabolism Liver

Half life 58 days (range 15-142 days)

Excretion Epithelial cells

Therapeutic considerations

Pregnancy cat. D(US)

Legal status P*rescription only*

Routes oral or intravenous

Amiodarone belongs to a class of drugs called Vaughan-Williams Class III antiarrhythmic agent. It is used in the treatment of a wide range of cardiac tachyarhthmias, including both ventricular and supraventricular (atrial) arrhythmias.

History

Amiodarone was initially developed in 1961 in Belgium as a treatment for angina. It was widely used throughout Europe as an anti-anginal medication, and was soon found to suppress arrhythmias.

Dr. Bramah Singh determined that amiodarone and sotalol belonged to a new class of antiarrhythmic agents (what would become the class III antiarrhythmic agents) that would prolong repolarization of the cardiac action potential. Based on this, the Argentinian physician Dr. Mauricio Rosenbaum began using amiodarone to treat his patients who suffered from supraventricular and ventricular arrhythmias, with impressive results. Based on papers written by Dr. Rosenbaum, physicians in the United States began prescribing amiodarone to their patients with potentially life-threatening arrhythmias in the late 1970s. By that time, amiodarone was commonly prescribed throughout Europe for the treatment of arrhythmias. Because amiodarone was not approved by the Food and Drug Administration for use in the United States at the time, physicians were forced to directly obtain amiodarone from pharmaceutical companies in Canada and Europe.

The FDA was reluctant to officially approve the use of amiodarone, since initial reports had shown increased incidence of serious pulmonary side-effects of the drug. In the mid 1980s, the European pharmaceutical companies began putting pressure on the FDA to approve amiodarone by threatening to cut the supply to the American physicians if it was not approved. In December of 1985, amiodarone was approved by the FDA for the treatment of arrhythmias. This makes amiodarone one of the few drugs approved by the FDA without rigorous randomized clinical trials.

Dosing

Amiodarone is available in oral and intravenous formulations.

Orally, it is available under the trade names *Pacerone®* (produced by Upsher-Smith Laboratories, Inc.) and *Cordarone®* (produced by Wyeth-Ayerst Laboratories) in 200mg and 400mg tablets; It is also available under the trade name *Aratac®* in 100mg and 200mg tablets in Australia and New Zealand.

It is also available in intravenous ampules and vials, typically in 150mg increments.

The dose of amiodarone administered is tailored to the individual and the dysrhythmia that is being treated. When administered orally, the bioavailability of amiodarone is quite variable. Absorption ranges from 22 to 95%, with better absorption when it is given with food.[1]

Amiodarone is fat-soluble, and tends to concentrate in tissues including fat, muscle, liver, lungs, and skin. This confers a high volume of distribution (5000 liters in a 70kg adult) and a long half-life. Due to the long half-life of amiodarone, oral loading typically takes days to weeks.

An oral loading dose is typically a total of 10 grams, divided over one to two weeks. Once an individual is loaded, a typical maintenance dose of amiodarone is 100 or 200 mg either once or twice daily.

An intravenous loading dose is typically 300mg in 20-30cc D5W for cardiac arrest. The loading infusion for dysrhythmias is typically 150mg in a 100cc bag of D5W given over 10 minutes. Both can be followed by a 360mg slow infusion over 6 hours then a maintenance infusion of 540mg over 18 hours.

Mechanism of action

Amiodarone is categorized as a class III antiarrhythmic agent, and prolongs phase 3 of the cardiac action potential. It has numerous other effects however, including actions that are similar to those of antiarrhythmic classes Ia, II, and IV.

Amiodarone shows beta blocker-like and calcium channel blocker-like actions on the SA and AV nodes, increases the refractory period via sodium- and potassium-channel effects, and slows intra-cardiac conduction of the cardiac action potential, via sodium-channel effects.

Indications for use

Because amiodarone has a low incidence of pro-arrhythmic effects, it has been used both in the treatment of acute life-threatening arrhythmias as well as the chronic suppression of arrhythmias. It is useful both in supraventricular arrhythmias and ventricular arrhythmias.

Ventricular fibrillation

The treatment of choice for ventricular fibrillation (VF) is electrical defibrillation. However amiodarone can be useful in shock-refractory VF. In the ARREST trial, amiodarone was shown to improve survival to hospital admission (when compared to placebo) in individuals who suffer cardiac arrest with shock-refractory VF.[2] It is on the basis of this study that the guidelines created by the American Heart Association for the treatment of VF include amiodarone as a second line agent (after epinephrine or vasopressin). ARREST was not adequately powered to demonstrate survival to hospital discharge.

Ventricular tachycardia

Amiodarone may be used in the treatment of ventricular tachycardia in certain instances. Individuals with hemodynamically unstable ventricular tachycardia should not initially receive amiodarone. These individuals should be defibrillated out of their unstable rhythm.

Amiodarone can be used in individuals with hemodynamically stable ventricular tachycardia. In these cases, amiodarone can be used regardless of the individual's underlying heart function and the type of ventricular tachycardia; it can be used in individuals with monomorphic ventricular tachycardia as well as individuals with polymorphic ventricular tachycardia. The dose of amiodarone is 150 mg IV administered over 10 minutes.

Atrial fibrillation

Individuals who have undergone open heart surgery are at an increased risk of developing atrial fibrillation (or AF) in the first few days post-procedure. In the ARCH trial, intravenous amiodarone (2 grams administered over 2 days) has been shown to reduce the incidence of atrial fibrillation after open heart surgery when compared to placebo.[3] However, clinical studies have failed to demonstrate long-term efficacy and have shown potentially fatal side effects such as pulmonary toxicities. While Amiodarone is not approved for AF by the FDA, it is a commonly prescribed off-label treatment due to the lack of efficacious treatment alternatives.

Contraindications

The only absolute contraindications to the administration of amiodarone is allergic reaction (ie: anaphylaxis) to the compound. However, because of the wide spectrum of the mechanism of action of amiodarone and the numerous side effects possible, there are a number of groups for which care should be taken when administering the drug.

Individuals who are pregnant or may become pregnant are strongly advised to not take amiodarone. Since amiodarone can be expressed in breast milk, women taking amiodarone are advised to stop nursing.

It is contraindicated in individuals with sinus nodal bradycardia, atrioventricular block, and second or third degree heart block who do not have an artificial pacemaker.

Individuals with baseline depressed lung function should be monitored closely if amiodarone therapy is to be initiated.

The injection should not be given to neonates, because the benzyl alcohol it contains may cause the fatal "gasping syndrome".

Metabolism

Amiodarone is extensively metabolized in the liver, and can affect the metabolism of numerous other drugs. The major metabolite of amiodarone is desethylamiodarone (DEA), which also has antiarrhythmic properties. The metabolism of amiodarone is inhibited by grapefruit juice, leading to elevated serum levels of amiodarone.

Interactions with other drugs

The pharmacokinetics of numerous drugs, including many that are commonly administered to individuals with heart disease, are affected by amiodarone. Particularly, doses of digoxin should be halved in individuals taking amiodarone.

Amiodarone potentiates the action of warfarin. Individuals taking both of these medications should have their warfarin dose halved and their anticoagulation status (measured as prothrombin time (PT) and international normalized ratio (INR)) measured more frequently. The effect of amiodarone in the warfarin concentration can be as early as a few days after initiation of treatment, or can be delayed a few weeks.

Amiodarone inhibits the action of the cytochrome P450 isozyme family. This reduces the clearance of many drugs, including the following: -

- Ciclosporin
- Digoxin
- Flecainide
Procainamide
Quinidine
- Sildenafil
- Simvastatin
- Theophylline
- Warfarin

Excretion

Unlike most other drugs, which are excreted via the urine or feces, amiodarone is excreted via shedding of epithelial cells. This includes loss of skin cells and loss of the cells of the lining of the gastrointestinal system. While the human body sheds millions of cells a day, the amount of amiodarone lost per day is small, giving a long half life (13 to 103 days). Therefore, if an individual was taking amiodarone on a chronic basis, if it is stopped it will remain in the system for months.

Side effects

Amiodarone has numerous side effects. Most individuals administered amiodarone on a chronic basis will experience at least one side effect.

Thyroid

Due to the iodine content of the agent (37.3% by weight), abnormalities in thyroid function are common. Amiodarone is structurally similar to thyroxine (a thyroid hormone), which contributes to the effects of amiodarone on thyroid function. The incidence of hypothyroidism is about 6%, while the incidence of hyperthyroidism is about 2%. They are called Wolff-Chaikoff effect and Jodbasedow effect separately.

Measurement of free thyroxine (FT4) alone may be unreliable and thyroid-stimulating hormone (TSH) should therefore also be checked every 6 months [4].

Thyroid uptake measurements (I-123 or I-131), which are used to differentiate causes of hyperthyroidism, are generally unreliable in patients who have been taking amiodarone. Because of the high iodine content of amiodarone, the thyroid gland is effectively saturated, thus preventing further uptake of isotopes of iodine.

Eye

Corneal micro-deposits (Corneal verticillata, also called vortex keratopathy) are almost universally present (over 90%) in individuals taking amiodarone for at least 6 months. These deposits typically do not cause any symptoms. About 1 in 10 individuals may complain of a blueish halo. Optic neuropathy occurs in 1-2% of people and is not dosage dependent. Bilateral optic disk swelling and mild and reversible visual field defects can also occur.

Gastrointestinal system

Liver toxicity due to amiodarone is quite rare. A drug-induced hepatitis (inflammation of the liver) may occur and is sometimes reversible by lowering the dose.

Skin

Long-term administration of amiodarone is associated with a blue-grey discoloration of the skin, "smurf syndrome." This is more commonly seen in individuals with lighter skin tones. The discoloration may revert upon cessation of the drug. However, the skin color may not return completely to normal.

Individuals taking amiodarone may become more sensitive to the harmful effects of UV-A light. Taking sunblock that also blocks UV-A rays appears to prevent this side effect.

Lung

The most serious reaction that is due to amiodarone is idiopathic pulmonary fibrosis. The incidence of pulmonary fibrosis is not dose related. Some individuals were noted to develop pulmonary fibrosis after a week of treatment, while others did not develop it after years of continuous use. There are no known factors that increase the incidence of amiodarone-induced pulmonary fibrosis in a particular individual. Common practice is to avoid the agent if possible in individuals with decreased lung function.

The most specific test of pulmonary toxicity due to amiodarone is a dramatically decreased DLCO noted on pulmonary function testing.

See also

- Antiarrhythmic agents

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Antiasthmatic drugs - Asthma

Bronchial Asthma

Classifications and external resources

ICD-10

J45.

ICD-9

493

OMIM

600807

DiseasesDB

1006

MedlinePlus

000141

eMedicine

med/177 emerg/43

MeSH

C08.127.108

Asthma is a disease of the respiratory system in which the airways constrict, become inflamed, and are lined with excessive amounts of mucus, often in response to one or more "triggers," such as exposure to an environmental stimulant (or allergen), cold air, exercise, or emotional stress. In children, the most common triggers are viral illnesses such as those that cause the common cold.[1] This airway narrowing causes symptoms such as wheezing, shortness of breath, chest tightness, and coughing, which respond to bronchodilators. Between episodes, most patients feel fine.

The disorder is a chronic or recurring inflammatory condition in which the airways develop increased responsiveness to various stimuli, characterized by bronchial hyper-responsiveness, inflammation, increased mucus production, and intermittent airway obstruction. The symptoms of asthma, which can range from mild to life threatening, can usually be controlled with a combination of drugs and enviromental changes.

Public attention in the developed world has recently focused on asthma because of its rapidly increasing prevalence, affecting up to one in four urban children.[2] Susceptibility to asthma can be explained in part by genetic factors, but no clear pattern of inheritance has been found. Asthma is a complex disease that is influenced by multiple genetic, developmental, and environmental factors, which interact to produce the overall condition.

History

The word asthma is derived from the Greek aazein, meaning "sharp breath." The word first appears in Homer's Iliad;[3] Hippocrates was the first to use it in reference to the medical condition. Hippocrates thought that the spasms associated with asthma were more likely to occur in tailors, anglers, and metalworkers. Six centuries later, Galen wrote much about asthma, noting that it was caused by partial or complete bronchial obstruction. Moses Maimonides, an influential medieval rabbi, philosopher, and physician, wrote a treatise on asthma, describing its prevention, diagnosis, and treatment.[4] In the 17th century, Bernardino Ramazzini noted a connection between asthma and organic dust. The use of bronchodilators started in 1901, but it was not until the 1960s that the inflammatory component of asthma was recognized, and anti-inflammatory medications were added to the regimen.

Signs and symptoms

In some individuals asthma is characterized by chronic respiratory impairment. In others it is an intermittent illness marked by episodic symptoms that may result from a number of triggering events, including upper respiratory infection, airborne allergens, and exercise.

An acute exacerbation of asthma is referred to as an asthma attack. The clinical hallmarks of an attack are shortness of breath (dyspnea) and either wheezing or stridor. Although the latter is "often regarded as the sine qua non of asthma,"[5] some victims present primarily with coughing, and in the late stages of an attack, air motion may be so impaired that no wheezing may be heard. When present the cough may sometimes produce clear sputum. The onset may be sudden, with a sense of constriction in the chest, breathing becomes difficult, and wheezing occurs (primarily upon expiration, but can be in both respiratory phases).

Signs of an asthmatic episode or asthma attack are either stridor or wheezing, rapid breathing (tachypnea), prolonged expiration, a rapid heart rate (tachycardia), rhonchous lung sounds (audible through a stethoscope), and over-inflation of the chest. During a serious asthma attack, the accessory muscles of respiration (sternocleidomastoid and scalene muscles of the neck) may be used, shown as in-drawing of tissues between the ribs and above the sternum and clavicles, and the presence of a paradoxical pulse (a pulse that is weaker during inhalation and stronger during exhalation).

During very severe attacks, an asthma sufferer can turn blue from lack of oxygen, and can experience chest pain or even loss of consciousness. Severe asthma attacks may lead to respiratory arrest and death. Despite the severity of symptoms during an asthmatic episode, between attacks an asthmatic may show few signs of the disease.

Diagnosis

In most cases, a physician can diagnose asthma on the basis of typical findings in a patient's clinical history and examination. Asthma is strongly suspected if a patient suffers from eczema or other allergic conditions—suggesting a general atopic constitution—or has a family history of asthma. While measurement of airway function is possible for adults, most new cases are diagnosed in children who are unable to perform such tests. Diagnosis in children is based on a careful compilation and analysis of the patient's medical history and subsequent improvement with an inhaled bronchodilator medication. In adults, diagnosis can be made with a peak flow meter (which tests airway restriction), looking at both the diurnal variation and any reversibility following inhaled bronchodilator medication.

Testing peak flow at rest (or baseline) and after exercise can be helpful, especially in young asthmatics who may experience only exercise-induced asthma. If the diagnosis is in doubt, a more formal lung function test may be conducted. Once a diagnosis of asthma is made, a patient can use peak flow meter testing to monitor the severity of the disease.

Differential diagnosis

Before diagnosing someone as asthmatic, alternative possibilities should be considered. A physician taking a history should check whether the patient is using any known bronchoconstrictors (substances that cause narrowing of the airways, e.g., certain anti-inflammatory agents or beta-blockers).

Chronic obstructive pulmonary disease, which closely resembles asthma, is correlated with more exposure to cigarette smoke, an older patient, less symptom reversibility after bronchodilator administration (as measured by spirometry), and decreased likelihood of family history of atopy.

Pulmonary aspiration, whether direct due to dysphagia (swallowing disorder) or indirect (due to acid reflux), can show similar symptoms to asthma. However, with aspiration, fevers might also indicate aspiration pneumonia. Direct aspiration (dysphagia) can be diagnosed by performing a Modified Barium Swallow test and treated with feeding therapy by a qualified speech therapist. If the aspiration is indirect (from acid reflux) then treatment directed at this is indicated.

Only a minority of asthma sufferers have an identifiable allergy trigger. The majority of these triggers can often be identified from the history; for instance, asthmatics with hay fever or pollen allergy will have seasonal symptoms, those with allergies to pets may experience an abatement of symptoms when away from home, and those with occupational asthma may improve during leave from work. Occasionally, allergy tests are warranted and, if positive, may help in identifying avoidable symptom triggers.

After pulmonary function has been measured, radiological tests, such as a chest X-ray or CT scan, may be required to exclude the possibility of other lung diseases. In some people, asthma may be triggered by gastroesophageal reflux disease, which can be treated with suitable antacids. Very occasionally, specialized tests after inhalation of methacholine — or, even less commonly, histamine — may be performed.

Asthma is categorized by the United States National Heart, Lung and Blood Institute as falling into one of four categories: mild intermittent, mild persistent, moderate persistent and severe persistent. The diagnosis of "severe persistent asthma" occurs when symptoms are continual with frequent exacerbations and frequent nighttime symptoms, result in limited physical activity and when lung function as measured by PEV or FEV1 tests is less than 60% predicted with PEF variability greater than 30%.

There is no cure for asthma. Doctors have only found ways to prevent attacks and relieve the symptoms such as tightness of the chest and trouble breathing.

Pathophysiology

Bronchoconstriction

In essence, asthma is the result of an immune response in the bronchial airways.[6]

The airways of asthmatics are "hypersensitive" to certain triggers, also known as stimuli (see below). In response to exposure to these triggers, the bronchi (large airways) contract into spasm (an "asthma attack"). Inflammation soon follows, leading to a further narrowing of the airways and excessive mucus production, which leads to coughing and other breathing difficulties.

There are several categories of stimuli:

- allergenic air pollution, from nature, typically inhaled, which include waste from common household insects, such as the house dust mite and cockroach, grass pollen, mould spores and pet epithelial cells;
- medications**, including** aspirin[7] **and** ^{2}-adrenergic antagonists **(beta blockers);**
- Use of fossil fuel related allergenic air pollution, such as ozone, Smog, Summer smog, nitrogen dioxide, and sulfur dioxide, which is thought to be one of the major reasons for the high prevalence of asthma in urban areas;
- various industrial compounds and other chemicals, notably sulfites; chlorinated swimming pools generate chloramines—monochloramine (NH_2Cl), dichloramine ($NHCl_2$) and trichloramine (NCl_3)—in the air around them, which are known to induce asthma.[8]
- early childhood infections, especially viral respiratory infections. However, persons of any age can have asthma triggered by colds and other respiratory infections even though their normal stimuli might be from another category (e.g. pollen) and absent at the time of infection. 80% of asthma attacks in adults and 60% in children are caused by respiratory viruses.

- exercise, the effects of which differ somewhat from those of the other triggers;
- (in some countries) - allergenic indoor air pollution from Newsprint & other literature such as, junk mail leaflets & glossy magazines.
- emotional stress which is poorly understood as a trigger. Perhaps because crying might be a form of exercise or because being given an asthma attack may be distressing.

Bronchial inflammation

The mechanisms behind allergic asthma—i.e., asthma resulting from an immune response to inhaled allergens—are the best understood of the causal factors. In both asthmatics and non-asthmatics, inhaled allergens that find their way to the inner airways are ingested by a type of cell known as antigen presenting cells, or APCs. APCs then "present" pieces of the allergen to other immune system cells. In most people, these other immune cells (TH0 cells) "check" and usually ignore the allergen molecules. In asthmatics, however, these cells transform into a different type of cell (TH2), for reasons that are not well understood. The resultant TH2 cells activate an important arm of the immune system, known as the humoral immune system. The humoral immune system produces antibodies against the inhaled allergen. Later, when an asthmatic inhales the same allergen, these antibodies "recognize" it and activate a humoral response. Inflammation results: chemicals are produced that cause the airways to constrict and release more mucus, and the cell-mediated arm of the immune system is activated. The inflammatory response is responsible for the clinical manifestations of an asthma attack. The following section describes this complex series of events in more detail.

Pathogenesis

The fundamental problem in asthma appears to be immunological: young children in the early stages of asthma show signs of excessive inflammation in their airways. Epidemiological findings give clues as to the pathogenesis: the incidence of asthma seems to be increasing worldwide, and asthma is now very much more common in affluent countries.

In 1968 Andor Szentivanyi first described The Beta Adrenergic Theory of Asthma; in which blockage of the Beta-2 receptors of pulmonary smooth muscle cells causes asthma.[9] Szentivanyi's Beta Adrenergic Theory is a citation classic[10] and has been cited more times than any other article in the history of the Journal of Allergy.

In 1995 Szentivanyi and colleagues demonstrated that IgE blocks beta-2 receptors.[11] Since overproduction of IgE is central to all atopic diseases, this was a watershed moment in the world of Allergy.[12]

The Beta-Adrenergic Theory has been cited in the scholarship of such noted investigators as Richard F. Lockey (former President of The American Academy of Allergy, Asthma, and Immunology),[13] Charles Reed (Chief of Allergy at Mayo Medical School),[14] and Craig Venter (Human Genome Project).[15]

One theory of pathogenesis is that asthma is a disease of hygiene. In nature, babies are exposed to bacteria and other antigens soon after birth, "switching on" the TH1 lymphocyte cells of the immune system that deal with bacterial infection. If this stimulus is insufficient—as it may be in modern, clean environments—then TH2 cells predominate, and asthma and other allergic diseases may develop. This "hygiene hypothesis" may explain the increase in asthma in affluent populations. The TH2 lymphocytes and eosinophil cells that protect us against parasites and other infectious agents are the same cells responsible for the allergic reaction. The Charcot-Leyden crystals are formed when the crystalline material in eosinophils coalesce. These crystals are significant in sputum samples of people with asthma. In the developed world, these parasites are now rarely encountered, but the immune response remains and is wrongly triggered in some individuals by certain allergens.

Another theory is based on the correlation of air pollution and the incidence of asthma. Although it is well known that substantial exposures to certain industrial chemicals can cause acute asthmatic episodes, it has not been proven that air pollution is responsible for the development of asthma. In Western Europe, most atmospheric pollutants have fallen significantly over the last 40 years, while the prevalence of asthma has risen.

Finally, it has been postulated that some forms of asthma may be related to infection, in particular by Chlamydia pneumoniae.[16] This issue remains controversial, as the relationship is not borne out by meta-analysis of the research.[17] The correlation seems to be not with the onset, but rather with accelerated loss of lung function in adults with new onset of non-atopic asthma.[18] One possible explanation is that some asthmatics may have altered immune response that facilitates long-term chlamydia pneumonia infection.[19] The response to targeting with macrolide antibiotics has been investigated, but the temporary benefit reported in some studies may reflect just their anti-inflammatory activities rather than their antimicrobic action.[17]

Asthma and sleep apnea

It is recognized with increasing frequency, that patients who have both obstructive sleep apnea (OSA) and bronchial asthma, often improve tremendously when the sleep apnea is diagnosed and treated.[20] CPAP is not effective in patients with nocturnal asthma only.[21]

Asthma and gastro-esophageal reflux disease

If gastro-esophageal reflux disease is present, the patient may have repetitive episodes of acid aspiration, which results in airway inflammation and "irritant-induced" asthma. GERD may be common in difficult-to-control asthma, but generally speaking, treating it does not seem to affect the asthma.[22]

Treatment

The most effective treatment for asthma is identifying triggers, such as pets or aspirin, and limiting or eliminating exposure to them. Desensitization to allergens has been shown to be a treatment option for certain patients.[23]

As is common with respiratory disease, smoking adversely affects asthmatics in several ways, including an increased severity of symptoms, a more rapid decline of lung function, and decreased response to preventive medications.[24] Asthmatics who smoke typically require additional medications to help control their disease. Furthermore, exposure of both nonsmokers and smokers to secondhand smoke is detrimental, resulting in more severe asthma, more emergency room visits, and more asthma-related hospital admissions.[25] Smoking cessation and avoidance of secondhand smoke is strongly encouraged in asthmatics.[26]

The specific medical treatment recommended to patients with asthma depends on the severity of their illness and the frequency of their symptoms. Specific treatments for asthma are broadly classified as relievers, preventers and emergency treatment. The Expert panel report 2: Guidelines for the diagnosis and management of asthma (EPR-2)[26] of the U.S. National Asthma Education and Prevention Program, and the British guideline on the management of asthma[27] are broadly used and supported by many doctors. Bronchodilators are recommended for short-term relief in all patients. For those who experience occasional attacks, no other medication is needed. For those with mild persistent disease (more than two attacks a week), low-dose inhaled glucocorticoids or alternatively, an oral leukotriene modifier, a mast-cell stabilizer, or theophylline may be administered. For those who suffer daily attacks, a higher dose of glucocorticoid in conjunction with a long-acting inhaled ^{2}-2 agonist may be prescribed; alternatively, a leukotriene modifier or theophylline may substitute for the ^{2}-2 agonist. In severe asthmatics, oral glucocorticoids may be added to these treatments during severe attacks.

For those in whom exercise can trigger an asthma attack (exercise-induced asthma), higher levels of ventilation and cold, dry air tend to exacerbate attacks. For this reason, activities in which a patient breathes large amounts of cold air, such as skiing and running, tend to be worse for asthmatics, whereas swimming in an indoor, heated pool, with warm, humid air, is less likely to provoke a response.[5]

Researchers at Harvard Medical School (HMS) have come up with convincing evidence that the answer to what causes asthma lies in a special type of natural "killer" cell. This finding means that physicians may not be treating asthma sufferers with the right kinds of drugs. For example, natural killer T cells seem to be resistant to the corticosteroids in widely used inhalers.[28]

Relief medication

Symptomatic control of episodes of wheezing and shortness of breath is generally achieved with fast-acting bronchodilators. These are typically provided in pocket-sized, metered-dose inhalers (MDIs). In young sufferers, who may have difficulty with the coordination necessary to use inhalers, or those with a poor ability to hold their breath for 10 seconds after inhaler use (generally the elderly), an asthma spacer (see top image) is used. The spacer is a plastic cylinder that mixes the medication with air in a simple tube, making it easier for patients to receive a full dose of the drug and allows for the active agent to be dispersed into smaller, more fully inhaled bits. A nebulizer—which provides a larger, continuous dose—can also be used. Nebulizers work by vaporizing a dose of medication in a

saline solution into a steady stream of foggy vapour, which the patient inhales continuously until the full dosage is administered. There is no clear evidence, however, that they are more effective than inhalers used with a spacer. Nebulizers may be helpful to some patients experiencing a severe attack. Such patients may not be able to inhale deeply, so regular inhalers may not deliver medication deeply into the lungs, even on repeated attempts. Since a nebulizer delivers the medication continuously, it is thought that the first few inhalations may relax the airways enough to allow the following inhalations to draw in more medication.

Relievers include:

- Short-acting, selective beta2-adrenoceptor agonists, such as salbutamol (albuterol USAN), levalbuterol, terbutaline and bitolterol. Tremors, the major side effect, have been greatly reduced by inhaled delivery, which allows the drug to target the lungs specifically; oral and injected medications are delivered throughout the body. There may also be cardiac side effects at higher doses (due to Beta-1 agonist activity), such as elevated heart rate or blood pressure; with the advent of selective agents, these side effects have become less common. Patients must be cautioned against using these medicines too frequently, as with such use their efficacy may decline, producing desensitization resulting in an exacerbation of symptoms which may lead to refractory asthma and death.
- Older, less selective adrenergic agonists, such as inhaled [29][30] When used solely as a relief medication, inhaled epinephrine has been shown to be an effective agent to terminate an acute asthmatic exacerbation.[29] In emergencies, these drugs were sometimes administered by injection. Their use via injection has declined due to related adverse effects.
- Anticholinergic medications, such as ipratropium bromide may be used instead. They have no cardiac side effects and thus can be used in patients with heart disease; however, they take up to an hour to achieve their full effect and are not as powerful as the $^{2}\boldsymbol{2}$-adrenoreceptor agonists.

Prevention medication

Current treatment protocols recommend prevention medications such as an inhaled corticosteroid, which helps to suppress inflammation and reduces the swelling of the lining of the airways, in anyone who has frequent (greater than twice a week) need of relievers or who has severe symptoms. If symptoms persist, additional preventive drugs are added until the asthma is controlled. With the proper use of prevention drugs, asthmatics can avoid the complications that result from overuse of relief medications.

Asthmatics sometimes stop taking their preventive medication when they feel fine and have no problems breathing. This often results in further attacks, and no long-term improvement.

Preventive agents include the following.

- Inhaled glucocorticoids (ciclesonide, fluticasone, budesonide, beclomethasone, mometasone, flunisolide, and triamcinolone).
- Leukotriene modifiers (montelukast, zafirlukast, pranlukast, and zileuton).

- Mast cell stabilizers (cromoglicate (cromolyn), and nedocromil).
- Antimuscarinics/anticholinergics (ipratropium, oxitropium, and tiotropium), which have a mixed reliever and preventer effect. (These are rarely used in preventive treatment of asthma, except in patients who do not tolerate beta-2-agonists.)
- Methylxanthines (theophylline and aminophylline), which are sometimes considered if sufficient control cannot be achieved with inhaled glucocorticoids and long-acting ^{2}-agonists alone.
- Antihistamines, often used to treat allergic symptoms that may underlie the chronic inflammation. In more severe cases, hyposensitization ("allergy shots") may be recommended.
- Omalizumab, an IgE blocker; this can help patients with severe allergic asthma that does not respond to other drugs. However, it is expensive and must be injected.
- Methotrexate is occasionally used in some difficult-to-treat patients.
- If chronic acid indigestion (GERD) contributes to a patient's asthma, it should also be treated, because it may prolong the respiratory problem.

Long-acting 22-agonists

Long-acting bronchodilators (LABD) give a 12-hour effect, and are used to give a smoothed symptomatic effect (used morning and night). While patients report improved symptom control, these drugs do not replace the need for routine preventers, and their slow onset means the short-acting dilators may still be required. In November of 2005, the American FDA released a health advisory alerting the public to findings that show the use of Long-acting ^{2}***2***-agonists could lead to a worsening of symptoms, and in some cases death.[31]

Currently available long-acting beta2-adrenoceptor agonists include salmeterol, formoterol, bambuterol, and sustained-release oral albuterol. Combinations of inhaled steroids and long-acting bronchodilators are becoming more widespread; the most common combination currently in use is fluticasone/salmeterol (Advair in the United States, and Seretide in the UK).

A recent meta-analysis of the roles of long-acting beta-agonists may indicate a danger to asthma patients. "These agents can improve symptoms through bronchodilation at the same time as increasing underlying inflammation and bronchial hyper-responsiveness, thus worsening asthma control without any warning of increased symptoms," said Shelley Salpeter in a Cornel study. The study goes on to say that "Three common asthma inhalers containing the drugs salmeterol or formoterol may be causing four out of five U.S. asthma-related deaths per year and should be taken off the market".[32]

Emergency treatment

When an asthma attack is unresponsive to a patient's usual medication, other treatments are available to the physician or hospital:[33]

- oxygen to alleviate the hypoxia (but not the asthma per se) that results from extreme asthma attacks;
- nebulized salbutamol or terbutaline (short-acting beta-2-agonists), often combined with ipratropium (an anticholinergic);
- systemic steroids, oral or intravenous (prednisone, prednisolone, methylprednisolone, dexamethasone, or hydrocortisone)
- other bronchodilators that are occasionally effective when the usual drugs fail:
  - nonspecific beta-agonists, injected or inhaled (epinephrine, isoetharine, isoproterenol, metaproterenol);
  - anticholinergics, IV or nebulized, with systemic effects (glycopyrrolate, atropine);
  - methylxanthines (theophylline, aminophylline);
  - inhalation anesthetics that have a bronchodilatory effect (isoflurane, halothane, enflurane);
  - the dissociative anaesthetic ketamine, often used in endotracheal tube induction
  - magnesium sulfate, intravenous; and
- intubation and mechanical ventilation, for patients in or approaching respiratory arrest.

Alternative and complementary medicine

Many asthmatics, like those who suffer from other chronic disorders, use alternative treatments; surveys show that roughly 50% of asthma patients use some form of unconventional therapy.[34][35] There are little data to support the effectiveness of most of these therapies. A Cochrane systematic review of acupuncture for asthma found no evidence of efficacy.[36] A similar review of air ionisers found no evidence that they improve asthma symptoms or benefit lung function; this applied equally to positive and negative ion generators.[37] A study of "manual therapies" for asthma, including osteopathic, chiropractic, physiotherapeutic and respiratory therapeutic maneuvers, found no evidence to support their use in treating asthma;[38] these manoeuvres include various osteopathic and chiropractic techniques to "increase movement in the rib cage and the spine to try and improve the working of the lungs and circulation"; chest tapping, shaking, vibration, and the use of "postures to help shift and cough up phlegm." On the other hand, one meta-analysis found that homeopathy has a potentially mild benefit in reducing symptom intensity;[39] however, the number of patients involved in the analysis was small, and subsequent studies have not supported this finding.[40] Several small trials have suggested some benefit from various yoga practices, ranging from integrated yoga programs[41] —"yogasanas, Pranayama, meditation, and kriyas"—to sahaja yoga,[42] a form of meditation.

The Buteyko method, a Russian therapy based on breathing exercises, has been investigated with mixed degrees of effect shown. A randomized, controlled trial of just 39 patients in 1998, suggested that it may moderately reduce the need for beta-agonists among asthmatics, but found no objective improvement in lung function.[43] Whilst a trial in New

Zealand, 2003, showed reduced beta-agonist medication by 94% and inhaled steroid by 34% after just six weeks.[44]

Given that some research has identified a negative association between helminth infection (hookworm) and asthma and hay fever, some have suggested that hookworm infestation, although not medically sanctioned, would cure asthma. There is anectdotal evidence to support this.[45]

Prognosis

The prognosis for asthmatics is good, especially for children with mild disease. For asthmatics diagnosed during childhood, 54% will no longer carry the diagnosis after a decade. The extent of permanent lung damage in asthmatics is unclear. Airway remodelling is observed, but it is unknown whether these represent harmful or beneficial changes.[6] Although conclusions from studies are mixed, most studies show that early treatment with glucocorticoids prevents or ameliorates decline in lung function as measured by several parameters.[46] For those who continue to suffer from mild symptoms, corticosteroids can help most to live their lives with few disabilities. The mortality rate for asthma is low, with around 6000 deaths per year in a population of some 10 million patients in the United States.[5] Better control of the condition may help prevent some of these deaths.

Epidemiology

More than 6% of children in the United States have been diagnosed with asthma, a 75% increase in recent decades. The rate soars to 40% among some populations of urban children. Asthma is usually diagnosed in childhood. The risk factors for asthma include:

- a personal or family history of asthma or atopy;

triggers (see Pathophysiology above);
premature birth or low birth weight;
viral respiratory infection in early childhood;
maternal smoking;
being male, for asthma in prepubertal children; and
being female, for persistence of asthma into adulthood.

There is a reduced occurrence of asthma in people who were breast-fed as babies. Current research suggests that the prevalence of childhood asthma has been increasing. According to the Centers for Disease Control and Prevention's National Health Interview Surveys, some 9% of US children below 18 years of age had asthma in 2001, compared with just 3.6% in 1980 (see figure). The World Health Organization (WHO) reports that some 8% of the Swiss population suffers from asthma today, compared with just 2% some 25–30 years ago.[47] Although asthma is more common in affluent countries, it is by no means a problem restricted to the affluent; the WHO estimate that there are between 15 and 20 million asthmatics in India. In the U.S., urban residents, Hispanics, and African Americans are affected more than the population as a whole. Globally, asthma is responsible for around 180,000 deaths annually.[47]

On the remote South Atlantic island Tristan da Cunha, 50% of the population are asthmatics due to heredity transmission of a mutation in the gene CC16.

Socioeconomic factors

The incidence of asthma is higher among low-income populations within a society (even though it is more common in developed countries than developing countries), which in the western world are disproportionately minority, and more likely to live near industrial areas. Additionally, asthma has been strongly associated with the presence of cockroaches in living quarters, which is more likely in such neighbourhoods.[48]

The quality of asthma treatment varies along racial lines, likely because many low-income people cannot afford health insurance and because there is still a correlation between class and race. For example, black Americans are less likely to receive outpatient treatment for asthma despite having a higher prevalence of the disease. They are much more likely to have emergency room visits or hospitalization for asthma, and are three times as likely to die from an asthma attack compared to whites. The prevalence of "severe persistent" asthma is also greater in low-income communities compared with communities with better access to treatment.[49][50]

Asthma and athletics

Asthma appears to be more prevalent in athletes than in the general population. One survey of participants in the 1996 Summer Olympic Games showed that 15% had been diagnosed with asthma, and that 10% were on asthma medication.[51] These statistics have been questioned on at least two bases. Persons with mild asthma may be more likely to be diagnosed with the condition than others because even subtle symptoms may interfere with their performance and lead to pursuit of a diagnosis. It has also been suggested that some professional athletes who do not suffer from asthma claim to do so in order to obtain special permits to use certain performance-enhancing drugs.

There appears to be a relatively high incidence of asthma in sports such as cycling, mountain biking, and long-distance running, and a relatively lower incidence in weightlifting and diving. It is unclear how much of these disparities are from the effects of training in the sport, and from self-selection of sports that may appear to minimize the triggering of asthma.[51][52]

In addition, there exists a variant of asthma called exercise-induced asthma that shares many features with allergic asthma. It may occur either independently, or concurrent with the latter. Exercise studies may be helpful in diagnosing and assessing this condition.

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Bronchodilators

A *bronchodilator* is a medication intended to improve bronchial airflow. Treatment of bronchial asthma is the most common application of these drugs. They are also intended to help expand the airways and improve the breathing capacity of patients with emphysema, pneumonia and bronchitis. Pharmaceutically bronchodilators belong to ^{2}2 mimetics - they act on ^{2}2 receptors in bronchial smooth muscle and bronchial mucous membranes. Bronchodilators, particularly non-prescription ones, are often misused as stimulants. A common side effect of these medications is desensitization, which may produce refractory bronchospasm.

Bronchodilators are either short acting or long acting. Short-acting medications provide quick or "rescue" relief from acute bronchoconstriction. Long-acting bronchodilators help to control and prevent symptoms. The three types of prescription bronchodilating drugs are ^{2}2-agonists (short and long acting), anticholinergics (short acting), and theophylline (long acting). Also, cannabis has been shown to be significantly bronchodilating.**[1]**

Short-acting ^{2}2-agonists These are quick-relief or "rescue" medications that provide fast, temporary relief from asthma symptoms or flare-ups. These medications usually take effect within 20 minutes or less, and can last from four to six hours. These inhaled medications are best for treating sudden and severe or new asthma symptoms. Taken 15 to 20 minutes ahead of time, these medications can also prevent asthma symptoms triggered by exercise or exposure to cold air. Patients who regularly or frequently need to take short-acting ^{2}2-agonists should consult their doctor, as such usage indicates uncontrolled asthma, and their routine medications may need adjustment.

Long-acting ^{2}2-agonists These are long-term medications taken routinely in order to control and prevent bronchoconstriction. They are not intended for fast relief. These medications take longer to begin working, but relieve airway constriction for up to 12 hours.

- Inhaled - Commonly taken twice a day with an anti-inflammatory medication, they maintain open airways and prevent asthma symptoms, particularly at night.
- Oral - Long-acting albuterol is available in pill or syrup form.

Effective for 12 hours, albuterol is particularly helpful for nighttime asthma symptoms. Because this medication requires high dosing, there tend to be increased side effects. Therefore it is not commonly prescribed. Side effects include increased heart rate,

hyperactivity, feeling nervous, shaky, or over-excited, and very rarely, upset stomach or difficulty sleeping.

Anticholinergics Only available as an inhalant, ipratropium bromide relieves acute or new asthma symptoms. Because it has no effect on asthma symptoms when used alone, it is most often paired with a short-acting ^{2}2-agonist.While it is considered a relief or rescue medication, it can take a full hour to begin working. For this reason it plays a minor role in asthma treatment. Dry throat is the most common side effect. If the medication gets in contact with the eyes, it may cause blurred vision for a brief time.

Theophylline Available in oral and injectible form, theophylline is a long-acting bronchodilator that prevents asthma episodes.It is prescribed in severe cases of asthma or those that are difficult to control. It must be taken daily and doses cannot be missed. Blood tests are required to monitor therapy and to indicate when dosage adjustment is necessary.Side effects can include nausea, vomiting, diarrhea, stomach or headache, rapid or irregular heart beat, muscle cramps, nervous or jittery feelings, and hyperactivity. These symptoms may signal the need for an adjustment in your medication.It may promote acid reflux, also known as GERD, by relaxing the lower esophageal sphincter muscle. Some medications, such as seizure and ulcer medications and antibiotics containing erythromycin, can interfere with the way theopylline works. Coffee, tea, colas, cigarette smoking, and viral illnesses can all affect the action of theopylline and change it effectiveness. Communicate any change related to these factors to your doctor so that the dose can be altered to fit the new conditions.

Brand names of common bronchodilators :

- Ventolin (salbutamol)

Primatene (epinephrine)
Flixotide
Serevent
Accu-Hale
Albuterol

Epinephrine

Systematic (IUPAC) name

4-(1-hydroxy-
2-(methylamino)ethyl)benzene-1,2-diol

Identifiers

CAS number 51-43-4

ATC code A01**AD01** B02**BC09** C01**CA24** R01**AA14** R03**AA01** S01**EA01**

PubChem 838

DrugBank APRD00450

Chemical data

Formula $C_9H_{13}NO_3$

Mol. weight 183.204 g/mol

Pharmacokinetic data

Bioavailability **Nil (oral)**

Metabolism adrenergic synapse (MAO and COMT)

Half life 2 minutes

Excretion n/a

Therapeutic considerations

Pregnancy cat. $A_{(AU)}$ $C_{(US)}$

Legal status $S4_{(AU)}$ $POM_{(UK)}$ $_{-only(US)}$

Routes IV, IM, endotracheal

Epinephrine (INN) (IPA: [Ì[pjÈn[frYn]) or *adrenaline* (BAN) (IPA: [YÈdr[nYlYn]), sometimes spelled "epinephrin" or "adrenalin" respectively, is a hormone. Epinephrine is a catecholamine, a sympathomimetic monoamine derived from the amino acids phenylalanine and tyrosine. The Latin roots ad-+renes and the Greek roots epi-+nephros both literally mean "on/to the kidney" (referring to the adrenal gland, which secretes epinephrine). Epinephrine is sometimes shortened to *epi* in medical jargon. Epinephrine is now also used in EpiPens. EpiPens are long narrow auto-injectors that administer epinephrine.

In May 1886, William Bates reported the discovery of a substance produced by the adrenal gland in the New York Medical Journal. Epinephrine was isolated and identified in 1895 by Napoleon Cybulski, a Polish physiologist. The discovery was repeated in 1897 by John Jacob Abel. Jokichi Takamine discovered the same hormone in 1900, without knowing about the previous discovery. It was first artificially synthesized in 1904 by Friedrich Stolz.

Actions in the body

Epinephrine plays a central role in the short-term stress reaction—the physiological response to threatening, exciting or environmental stressor conditions such as high noise levels or bright light (see Fight-or-flight response). It is secreted by the adrenal medulla. When released into the bloodstream, epinephrine binds to multiple receptors and has numerous effects throughout the body. It increases heart rate and stroke volume, dilates the pupils, and constricts arterioles in the skin and gut while dilating arterioles in leg muscles. It elevates the blood sugar level by increasing depolymerization of glycogen to glucose in the

liver, and at the same time begins the breakdown of lipids in adipocytes. Epinephrine has a suppressive effect on the immune system.

Epinephrine is used as a drug to promote peripheral vascular resistance via alpha-stimulated vasoconstriction in cardiac arrest and other cardiac dysrhythmias resulting in diminished or absent cardiac output, such that blood is shunted to the body's core. This beneficial action comes with a significant negative consequence—increased cardiac irritability—which may lead to additional complications immediately following an otherwise successful resuscitation. Alternatives to this treatment include vasopressin, a powerful antidiuretic which also increases peripheral vascular resistance leading to blood shunting via vasoconstriction, but without the attendant increase to myocardial irritability.

Because of its suppressive effect on the immune system, epinephrine is used to treat anaphylaxis and sepsis. Allergy patients undergoing immunotherapy may receive an epinephrine rinse before the allergen extract is administered, thus reducing the immune response to the administered allergen. It is also used as a bronchodilator for asthma if specific beta2-adrenergic receptor agonists are unavailable or ineffective. Adverse reactions to epinephrine include palpitations, tachycardia, anxiety, headache, tremor, hypertension, and acute pulmonary edema.

A pheochromocytoma is a tumor of the adrenal gland (or, rarely, the ganglia of the sympathetic nervous system), which secretes excessive amounts of catecholamines, usually epinephrine.

Pharmacology

Epinephrine's actions are mediated through adrenergic receptors (sometimes referred to as adrenoceptors).

It binds to ±***1*** receptors of liver cells, which activate inositol-phospholipid signaling pathway, signaling the phosphorylation of insulin, leading to reduced ability of insulin to bind to its receptors.

Epinephrine also activates ^{2}-adrenergic receptors of the liver and muscle cells, thereby activating the adenylate cyclase signaling pathway, which will in turn increase glycogenolysis. ^{2}2 receptors are found primarily in skeletal muscle blood vessels where they do indeed trigger vasodilation. However Alpha receptors are found in most smooth muscles and splanchnic vessels, and epinephrine triggers vasoconstriction in those vessels. Thus, depending on the patient, administration of epinephrine may raise or lower blood pressure, depending whether or not the net increase or decrease in peripheral resistance can balance the positive inotropic and chronotropic effects of epinephrine on the heart.

Terminology

Although widely referred to as "adrenaline" outside of the US, and the lay public worldwide, the USAN and INN for this chemical is "epinephrine" because "adrenaline" bore too much similarity to the Parke, Davis & Co trademark "adrenalin" (without the "e") which was registered in the US.

The BAN and EP term for this chemical is "adrenaline", and is indeed now one of the few differences between the INN and BAN systems of names.

Amongst US health professionals the term epinephrine is generally used over adrenaline. However, it should be noted that when referring to pharmaceuticals that mimic the actions of epinephrine/adrenaline their receptor sites are universally referred to as "adrenergics".

Epinephrine also known as adrenaline can be found in nature in the R form; however, racemic mixtures of the molecule can be used if its chirality is destroyed.

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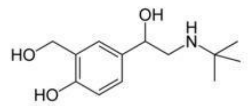
Salbutamol



Systematic (IUPAC) name

2-(hydroxymethyl)-4-[1-hydroxy-

2-(tert-butylamino)ethyl]phenol
Identifiers

CAS number 18559-94-9

ATC code R03**AC02** R03**CC02**

PubChem 2083

DrugBank APRD00553

Chemical data

Formula $C_{13}H_{21}NO_3$

Mol. weight 239.311

Pharmacokinetic data

Metabolism Hepatic

Half life 1.6 hours

Excretion Urinary

Therapeutic considerations

Pregnancy cat. $A_{(AU)}$ $C_{(US)}$

Legal status S3(AU) ?(CA) POM(UK) -only(US)

Routes Oral, inhalational, IV

Salbutamol (INN) or *albuterol* (USAN) is a short-acting ²2-adrenergic receptor agonist used for the relief of bronchospasm in conditions such as asthma and COPD.

Salbutamol sulfate is usually given by the inhaled route for direct effect on bronchial smooth muscle. This is usually achieved through a metered dose inhaler (MDI), nebuliser or other proprietary delivery devices (e.g. Rotahaler or Autohaler). Salbutamol can also be given orally or intravenously. However, some asthmatics may not respond to these medications as they will not have the required DNA base sequence in a specific gene.

Salbutamol became available in the United Kingdom in 1969 and in the United States in 1980 under the trade name *Ventolin*.

Clinical use

Salbutamol is specifically indicated in the following conditions:

- acute asthma
- symptom relief during maintenance therapy of asthma and other conditions with reversible airways obstruction (including COPD)
- protection against exercise-induced asthma
- hyperkalemia, especially in patients with renal failure
- can be aerosolized for patients with Cystic Fibrosis, along with ipratropium bromide and pulmozyme.

As a ^{2}***2***-agonist, salbutamol also finds use in obstetrics. Intravenous salbutamol can be used as a tocolytic to relax the uterine smooth muscle to delay premature labour. Whilst preferred over agents such as atosiban and ritodrine, its role has largely been replaced by the calcium-channel blocker nifedipine which is more effective, better tolerated and orally administered. (Rossi, 2004)

Mode of action

As with other ^{2}***2***-adrenergic receptor agonists, salbutamol binds to ^{2}***2***-adrenergic receptors with a higher affinity than ^{2}***1***-receptors. In the airway, activation of ^{2}2-receptors results in relaxation of bronchial smooth muscle resulting in a widening of the airway (bronchodilation). Inhaled salbutamol sulfate has a rapid onset of action, providing relief within 5-15 minutes of administration.

In tocolysis, the activation of ^{2}***2***-receptors results in relaxation of uterine smooth muscle, thus delaying labour.

Adverse effects

Whilst salbutamol is well-tolerated, particularly when compared with previous therapies such as theophylline, like all medications there exists the potential for adverse drug reactions to occur - especially when in high doses, or when taken orally or intravenously.

Common adverse effects include: tremor, palpitations and headache. (Rossi, 2004)

Infrequent adverse effects include: tachycardia, muscle cramps, agitation, hypokalemia, hyperactivity in children, and insomnia. (Rossi, 2004)

Other brand names

Salbutamol is sold under the brand names *Airomir*, *Asthalin*, *Asmol*, *Buventol*, *Proventil*, *Salamol*, *Sultanol*, *Ventolin* and *Volmax*.

References

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Theophylline

Systematic (IUPAC) name

1,3-dimethyl-7H-purine-2,6-dione

Identifiers

CAS number 58-55-9

ATC code R03**DA04**

PubChem 2153

DrugBank APRD00082

Chemical data

Formula $C_7H_8N_4O_2$

Mol. weight 180.164 g/mol

Pharmacokinetic data

Bioavailability **100%**

Protein binding 40%, primarily to albumin

Metabolism hepatic to 1-methyluric acid

Half life 8 hours

Therapeutic considerations

Pregnancy cat. $A_{(AU)}$ $C_{(US)}$

Legal status $P_{(UK)}$

Routes oral, IV

Theophylline is a methylxanthine drug used in therapy for respiratory diseases such as COPD or asthma under a variety of brand names. As a member of the xanthine family, it bears structural and pharmacological similarity to caffeine. It is naturally found in black tea and green tea.

The main actions of theophylline are:

- relaxing of bronchial smooth muscle

positive inotropic (increasing heart muscle contractility and efficiency)
positive chronotropic (increasing heart rate)
increase of blood pressure
increase of renal blood flow
some anti-inflammatory effects

History

Theophylline was first extracted from tea leaves around 1888 by the German biologist Albrecht Kossel. The drug was chemically identified in 1896 and eventually it was synthesized by another German scientist, Wilhelm Traube. Theophylline's first clinical use in asthma came in the 1950s.

Side effects

The use of theophylline is complicated by the fact that it interacts with various drugs, chiefly cimetidine and phenytoin, and that it has a narrow therapeutic index, so its use must be monitored to avoid toxicity. It can also cause nausea, diarrhea, increase in heart rate, arrhythmias and CNS excitation. Its toxicity is increased by erythromycin, cimetidine and fluoroquinolones.

The main therapeutic uses of theophylline are:

- chronic obstructive diseases of the airways
- chronic obstructive pulmonary disease (COPD)
- bronchial asthma.

A proposed mechanism of action includes a non-specific inhibition of phosphodiesterase enzymes, producing an increase in intracellular cyclic AMP; however, this is not known with certainty.[1][2][3]

Theophylline has been shown to inhibit TGF-beta mediated conversion of pulmonary fibroblasts into myofibroblasts in COPD and asthma via cAMP-PKA pathway and suppresses COL1 mRNA which codes for the protein collagen. (Yano, Biochem and Biophys Res Comm V341-3, 2006)

It has been shown that theophylline may reverse the clinical observations of steroid insensitivity in patients with COPD and asthmatics who are active smokers (a condition resulting in oxidative stress) via a distinctly separate mechanism. Theophylline in vitro can restore the reduced HDAC (histone deacetylase) activity that is induced by oxidative stress (i.e. in smokers), returning steroid responsiveness toward normal (Ito et al., 2002a).

Furthermore, theophylline has been shown to directly activate HDAC2 (Ito et al., 2002b). (Corticosteroids switch off the inflammatory response by blocking the expression of inflammatory mediators through deacetylation of histones, an effect mediated via histone deacetylase-2 (HDAC2). Once deacetylated, DNA is rewound around histones and repackaged so that the promoter regions of inflammatory genes are unavailable for binding of transcription factors such as NFkB that act to turn on inflammatory activity. It has recently been shown that the oxidative stress associated with cigarette smoke can inhibit the activity of HDAC2, thereby blocking the anti-inflammatory effects of corticosteroids.) Thus theophylline could prove to be a novel form of adjunct therapy in improving the clinical response to steroids in smoking asthmatics.

Mast cell stabilizers

Mast cell stabilizers are medications used to prevent or control certain allergic disorders. They block a calcium channel essential for mast cell degranulation, stabilizing the cell and so prevent the release of histamine and related mediators.

As inhalers thay are used to treat asthma, as nasal sprays to treat Hay fever (allergic rhinitis) and as eye drops for allergic conjunctivitis. Finally in oral form they are used to treat the rare condition of mastocytosis.

Anticholinergics

An *anticholinergic* agent is a member of a class of pharmaceutical compounds which serve to reduce the effects mediated by acetylcholine in the central nervous system and peripheral nervous system.

Anticholinergics are typically reversible competitive inhibitors of one of the two types of acetylcholine receptors, and are classified according to the receptors that are affected: *antimuscarinic* agents operate on the muscarinic acetylcholine receptors, and *antinicotinic* agents operate on the nicotinic acetylcholine receptors. The majority of anticholinergics are antimuscarinics.

Effects

When a significant amount of anticholinergic is taken into the body, a toxidrome known as *acute anticholinergic syndrome* may result. This may happen accidentally or intentionally as a form of recreational drug use. This class of drug is usually considered the least "fun" by experienced drug users, possibly due to the lack of euphoria caused by anticholinergics. Because most users do not enjoy the experience, they don't use it again, or very rarely. Risk of addiction is low in the anticholinergic class. Effects are usually more pronounced in the elderly, due to the decrease of acetylcholine production associated with age.

Possible effects of anticholinergics include:

- Ataxia; loss of coordination

Decreased mucus production in the nose and throat; consequent dry, sore throat
Xerostomia or dry mouth
Cessation of perspiration; consequent increased thermal dissipation through the skin leading to hot, red skin
Increased body temperature
Pupil dilation (mydriasis); consequent sensitivity to bright light (photophobia)
Loss of accommodation (loss of focusing ability, blurred vision — cycloplegia)
Double vision (diplopia)
Increased heart rate (tachycardia)
Urinary retention
Diminished bowel movement, sometimes ileus
Increased intraocular pressure, dangerous for people with narrow-angle glaucoma

Possible effects in the central nervous system resemble those associated with delirium, and may include:

- Confusion
- Disorientation
- Agitation
- Respiratory depression
- Short-term memory loss

- Inability to concentrate
- Wandering thoughts; inability to sustain a train of thought
- Incoherent speech
- Wakeful myoclonic jerking
- Unusual sensitivity to sudden sounds
- Illogical thinking
- Photophobia
- Visual disturbances
  - Periodic flashes of light
  - Periodic changes in visual field
  - Visual snow
  - Restricted or "tunnel vision"
- Visual, auditory, or other sensory hallucinations
  - Warping or waving of surfaces and edges
  - Textured surfaces
  - "Dancing" lines; "spiders", insects
  - Lifelike objects indistinguishable from reality
- Rarely: seizures, coma and death

Acute anticholinergic syndrome is completely reversible and subsides once all of the toxin has been excreted. Ordinarily, no specific treatment is indicated. However, in extreme cases, especially those that involves severe distortions of mental state, a reversible cholinergic agent such as physostigmine may be used.

Plant sources

The most common plants containing anticholinergic alkaloids are:

- Atropa belladonna (Deadly Nightshade)
Mandragora officinarum (Mandrake)
Hyoscamus niger (Henbane)
Datura species (Datura)

Pharmaceuticals

- Unclassified
  - benztropine (Cogentin®)
- Muscarinic receptor antagonists
  - Belladonna alkaloids
    - Scopolamine (L-Hyoscine)
    - Atropine (D/L-Hyoscyamine)
  - Synthetic and Semisynthetic
    - Dicyclomine

Flavoxate
Ipratropium
Oxybutynin

Pirenzepine
Tiotropium
Tolterodine (Detrusitol®)
Tropicamide
Solifenacin (Vesicare®)
Darifenacin (Enablex®)

- Nicotinic receptor antagonists
  - Ganglionic blocking agents
    - Trimethaphan
  - Nondepolarizing neuromuscular blocking agents
    - Atracurium

Doxacurium
Mivacurium
Pancuronium
Tubocurarine
Vecuronium

  - Depolarizing neuromuscular blocking agents

- Suxamethonium chloride

Many other drugs have anticholinergic properties, including cyclic antidepressants and the common allergy medications diphenhydramine (Benadryl) and its 8-chlorotheophylline salt dimenhydrinate (Dramamine), which are used medically for antihistaminergic and antiemetic purposes, and sometimes recreationally for their psychoactive effects. The common side effects of some SSRI antidepressants, such as Prozac (fluoxetine), often sweaty palms, are due to anticholinergic properties.

Some drugs, such as hydrocodone, are mixed with small amounts of an anticholinergic, such as Homatropine Methylbromide to discourage abuse.

Deliriants

The *deliriants* (or anticholinergics) are a special class of dissociatives which are antagonists for the acetylcholine receptors (unlike muscarine and nicotine which are agonists of these receptors). Deliriants are distinct from classical hallucinogens in that users will have conversations with people who aren't there, or become angry with a 'person' mimicking their actions, not realizing it is their own reflection in a mirror (a situation which could be dangerous if they became aggressive towards a glass mirror). The anticholinergics have effects akin to sleepwalking (particularly in that the subject has poor recall of the experience).

Included in this group are such Solanaceae plants as deadly nightshade, mandrake, henbane and datura (sometimes referred to as the Belladonna alkaloids), as well as a number of pharmaceutical drugs such as the antihistamine diphenhydramine (Benadryl) and the antiemetics dimenhydrinate (Dramamine or Gravol) and scopolamine.

In addition to the danger of being far more out of touch with reality than with other drugs, and retaining a truly fragmented dissociation from regular consciousness without being immobilized, the anticholinergics are toxic, can cause death due to overdose, and also include plenty of uncomfortable side effects including an intense drying effect where sweat, saliva, mucus and urination are prevented, as well as a pronounced dilation of the pupils which can last for several days resulting in sensitivity to light, blurry vision and inability to read.

Deliriants are common to European mythology, including the plants mandrake, deadly nightshade, and various datura species.

Pharmacological classes of deliriants, and their general subjective effects

Entries marked with a # are naturally occurring.

Tropanes

- Atropine #
- Scopolamine #
  - Hyoscyamine #
- 3-quinuclidinyl benzilate

Antihistaminics

- diphenhydramine (Benadryl) dimenhydrinate (Dramamine) cyclizine (Marezine or Marzine)

See also

- Anticholinergics
- Atropine
- Scopolamine
- Dissociative drug
- Psychedelics, Dissociatives and Deliriants
- Psychoactive drug

3-Quinuclidinyl benzilate

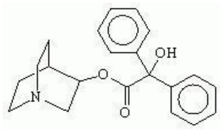


Diagram of a BZ molecule

3-quinuclidinyl benzilate (QNB), empirical formula C21H23NO3, full chemical name 1-azabicyclo[2.2.2]oct-3-yl ±-hydroxy-±-phenylbenzeneacetate, is an odorless military incapacitating agent. Its NATO code is *BZ*. The Iraqi incapacitating agent Agent 15 is believed either to be the same as or similar to BZ.

BZ is a glycolate anticholinergic compound related to atropine, scopolamine, hyoscyamine, and other deliriants. Dispersal would be as an aerosolized solid (primarily for inhalation) or as agent dissolved in one or more solvents for ingestion or percutaneous absorption.

Acting as a competitive inhibitor of acetylcholine at postsynaptic and postjunctional muscarinic receptor sites in smooth muscle, exocrine glands, autonomic ganglia, and the brain, BZ decreases the effective concentration of acetylcholine seen by receptors at these sites. Thus, BZ causes peripheral nervous system (PNS) effects that in general are the opposite of those seen in nerve agent poisoning. Central nervous system (CNS) effects include stupor, confusion, and confabulation with concrete and panoramic illusions and hallucinations, and with regression to automatic "phantom" behaviors such as plucking and disrobing.

Physostigmine, which increases the concentration of acetylcholine in synapses and in neuromuscular and neuroglandular junctions, is a specific antidote.

Production of BZ is controlled under schedule 2 of the Chemical Weapons Convention.

Development and military use

Following World War II, the United States military investigated a wide range of possible nonlethal, psychobehavioral chemical incapacitating agents to include psychedelic indoles such as lysergic acid diethylamide (LSD-25) and marijuana derivatives, certain tranquilizers like ketamine or fentanyl, as well as several glycolate anticholinergics. One of the anticholinergic compounds, 3-quinuclidinyl benzilate, was assigned the NATO code BZ and was weaponized at the beginning of the 1960s for possible battlefield use. This agent was reportedly employed by American troops as a counterinsurgency weapon in Vietnam, but supposedly otherwise never saw operational use. It has been rumored that BZ was administered to American troops in order to increase their fighting power and improve their performance, but this rumor is very disputed. This rumor is a major reference point in the film Jacob's Ladder (1990), although the film does not discuss BZ specifically. Destruction of American stockpiles began in 1988 and is now complete.

In February 1998, the British Ministry of Defense released an intelligence report that accused Iraq of having stockpiled large amounts of a glycolate anticholinergic incapacitating agent known as Agent 15. Agent 15 is an alleged Iraqi incapacitating agent that is likely to be chemically either identical to BZ or closely related to it. Agent 15 was reportedly stockpiled in large quantities prior to and during the Persian Gulf War. The combination of anticholinergic PNS and CNS effects aids in the diagnosis of patients exposed to these agents.

Also in 1998, there were allegations that elements of the Yugoslav People's Army used incapacitating agents against fleeing Bosnian refugees in 1995 that caused hallucinations and irrational behavior. [1] Physical evidence of BZ use in Bosnia remains elusive, however.

Sources other than military

BZ and related anticholinergic compounds can be synthesized in clandestine laboratories, but its illicit use is nonexistant, because of its unpleasant effects. 3-quinuclidinyl benzilate, called QNB in the scientific community, is used in pharmacology as a muscarinic receptor antagonist.

Physiochemical characteristics

BZ is odorless. It is stable in most solvents, with a half-life of three to four weeks in moist air; even heat-producing munitions can disperse it. It is extremely persistent in soil and water and on most surfaces. It is also soluble in propylene glycol, DMSO, and other solvents.

Detection and protection

Because BZ is odorless and nonirritating, and because clinical effects are not seen until after a latent period of 30 minutes to 24 hours, exposure could occur without the knowledge of casualties. No currently available field military or civilian detector is designed to disclose the presence of BZ or other anticholinergic compounds in the environment. Confirmation of the exact chemical involved in an incapacitating agent exposure would have to await laboratory analysis of environmental specimens containing the agent. The HEPA filter in the canister of the chemical protective mask prevents exposure of the face and respiratory tract to aerosolized BZ. The chemical protective ensemble protects the skin against contact with BZ or other incapacitating agents dispersed as fine solid particles or in solution. Protection against ingestion would depend upon a high index of suspicion for BZ contaminated food or drink.

Toxicokinetics

BZ may be dispersed as an aerosolized collection of small particles. Alternately, it may be dissolved in a solvent such as DMSO to enhance percutaneous absorption. Bioavailability via ingestion and by inhalation of particles 1 micrometre in size approximates 80%, and 40 to 50%, respectively, of a parenterally delivered dose of BZ. Percutaneous absorption of BZ dissolved in propylene glycol yields, after a latent period of up to 24 hours, serum levels approximately 5 to 10% of those achieved with intravenous or intramuscular administration. Although inhalation of aerosolized BZ is probably the greatest risk on the battlefield, terrorists may choose to disseminate BZ in forms that provide significant opportunities for ingestion and absorption through the skin.

Following absorption, BZ is systemically distributed to most organs and biological tissues of the body. Its ability to reach synapses and neuromuscular and neuroglandular junctions throughout the body is responsible for its PNS effects, whereas its ability to cross the blood-brain barrier confers upon it the ability to cause CNS effects. Atropine and hyoscyamine both cross the placenta and can be found in small quantities in breast milk; whether this is also true for BZ is unclear.

Metabolism of BZ would be expected to occur primarily in the liver, with elimination of unchanged agent and metabolites chiefly in the urine.

Toxicity

The characteristic that makes BZ an incapacitating rather than a toxic chemical warfare agent is its high safety ratio. The amount required to produce effects is a thousand or more fold less than a fatal dose of the compound. In terms of Ct products (admittedly a sometimes problematic way of measuring dosage received after aerosol exposure), the ICt50 (the Ct product needed to produce incapacitation in 50% of an exposed group) for BZ is 112 mg·min/m^3, whereas the Ld50 is estimated to be 200,000 mg·min/m^3.

Toxicodynamics (mechanism of action)

The agent BZ and other anticholinergic glycolates act as competitive inhibitors of the neurotransmitter acetylcholine neurons (1) at postjunctional muscarinic receptors in cardiac and smooth muscle and in exocrine (ducted) glands and (2) at postsynaptic receptors in neurons. As the concentration of BZ at these sites increases, the proportion of receptors available for binding to acetylcholine decreases and the end organ "sees" less acetylcholine. (One way of visualizing this process is to imagine BZ coating the surface of the end organ and preventing acetylcholine from reaching its receptors.) Because BZ has little to no agonist activity with respect to acetylcholine, high concentrations of BZ essentially substitute a "dud" for acetylcholine at these sites and lead to clinical effects reflective of understimulation of end organs.

Clinical effects

Peripheral Effects:

- Mydriasis, blurred vision

Dry mouth, skin

Initially rapid heart rate declining to normal or slow heart rate over time

Possible flushing of the skin

The PNS effects of BZ are, in general, readily understood as those of understimulation of end organs and are qualitatively similar to those of atropine. Decreased stimulation of eccrine and apocrine sweat glands in the skin results in dry skin (an affected patient can be "dry as a bone") and a reduction in the ability to dissipate heat by evaporative cooling. The skin becomes warm ("hot as a hare") partly from decreased sweating and partly from compensatory cutaneous vasodilatation (the patient becomes "red as a beet," with a so-called atropine flush) as the body attempts to shunt a higher proportion of core-temperature blood as close as possible to the surface of the skin. With decreased heat loss, the core temperature itself rises.

Understimulation of other exocrine glands leads to xerostomia (dry mouth, another way in which the patient is "dry as a bone"), thirst, and decreased secretions from lacrimal, nasal, bronchial, and gastrointestinal glands.

Decreased cholinergic stimulation of pupillary sphincter muscles allows alpha-adrenergically innervated pupillary dilating muscles to act essentially unopposed, resulting in mydriasis. (In fact, the cosmetic effect of mydriasis in women who applied extracts of deadly nightshade topically to their eyes explains the name "belladonna" given to this plant.) Similar effects on cholinergic ciliary muscles produce paralysis of accommodation. Classically, the patient is described as being "blind as a bat". Other smooth muscle effects from BZ intoxication include decreased bladder tone and decreased urinary force with possibly severe bladder distention (yet another way in which the patient may be said to be "dry as a bone").

BZ typically raises the heart rate initially, but hours later, depending on the dose of BZ, the heart rate falls to normal or may become slow. Either the peripheral vagal blockade has ceased or the stimulation of the vagal nucleus has occurred.

Neither atropine nor BZ can act directly at the postjunctional nicotinic receptors found in skeletal muscle, but BZ-exposed patients nonetheless exhibit muscle weakness. This weakness, along with incoordination, heightened stretch reflexes, and ataxia, is probably due to the effects of BZ at CNS sites.

The PNS effects of BZ are essentially side effects that are useful in diagnosis, but incidental to the CNS effects for which the incapacitating agents were developed. These CNS effects include a dose-dependent decrease in the level of consciousness, beginning with drowsiness and progressing through sedation to stupor and coma. The patient is often disoriented to time and place. Disturbances in judgment and insight appear. The patient may abandon socially imposed restraints and resort to vulgar and inappropriate behavior. Perceptual clues may no longer be readily interpretable, and the patient is easily distracted and may have memory loss, most notably short-term memory. In the face of these deficits, the patient still tries to make sense of his environment and will not hesitate to make up answers on the spot to questions that confuse him. Speech becomes slurred and often senseless, and loss of inflection produces a flat, monotonous voice. References become concrete and semiautomatic with colloquialisms, clichés, profanity, and perseveration. Handwriting also deteriorates. Semiautomatic behavior may also include disrobing (perhaps partly because of increased body temperature), mumbling, and phantom behaviors such as constant picking, plucking, or grasping motions ("woolgathering" or carphology).

It should be noted that BZ was supposedly administered to soldiers during the Vietnam War in the film Jacob's Ladder, but the specified effects are not accurate and possibly exaggerated. It has not been proven that BZ sends people exposed to it in a homicidal frenzy, as the film suggests.

Central effects

- Disturbances in level of consciousness

Misperceptions and difficulty in interpretation (delusions, hallucinations)
Poor judgment and insight (denial of illness)
Short attention span, distractibility, impaired memory (particularly recent)
Slurred speech, perseveration
Disorientation

Ataxia
Variability (quiet/restless)

Central nervous system mediated perceptual disturbances in BZ poisoning include both illusions (misidentification of real objects) and hallucinations (the perception of objects or attributes that have no objective reality). (Although the phrase "mad as a hatter" refers to poisoning from mercury formerly used by hatters on felt, it can just as well serve as a reminder of CNS effects from anticholinergics.) Hallucinations resulting from anticholinergics such as BZ tend to be realistic, distinct, easily identifiable (often commonly encountered objects or persons), panoramic, and difficult to distinguish from reality. They also have the tendency to decrease in size during the course of the intoxication. This is in contrast to the typically vague, ineffable, and transcendent-appearing hallucinations induced by psychedelics such as LSD.

Another prominent CNS finding in BZ poisoning is behavioral lability, with patients swinging back and forth between quiet confusion and self-absorption in hallucinations, to frank combativeness. Moreover, as other symptoms begin to resolve, intermittent paranoia may be seen. Automatic behaviors common during resolution include the crawling or climbing motions called "progresso obstinato" in old descriptions of dementia.

BZ produces effects not just in individuals, but also in groups. Sharing of illusions and hallucinations (folie à deux, folie en famille, and "mass hysteria") is exemplified by two BZ-intoxicated individuals who would take turns smoking an imaginary cigarette clearly visible to both of them but to no one else. [Clarification] When one observed subject mumbled, "Gotta cigarette?" His delirious companion held out an invisible pack, he followed with, "S'okay, don't wanna take your last one." In another test it was reported two victims of BZ played tennis with imaginary rackets.

Time course of effects

Clinical effects from ingestion or inhalation of BZ appear after an asymptomatic or latent period that may be as little as 30 minutes, or as long as 20 hours; the usual range is 0.5 to 4 hours, with a mean of 2 hours. However, effects may not appear up to 36 hours after skin exposure to BZ.

Once effects appear, their duration is typically 72 to 96 hours and are dose-dependent. Following an ICt50 of BZ, severe effects may last 36 hours, but mild effects may persist for an additional day.

The clinical course from BZ poisoning can be divided into the following four stages:

1. Onset or induction (zero to four hours after exposure), characterized by parasympathetic blockade and mild CNS effects.
2. Second phase (4 to 20 hours after exposure), characterized by stupor with ataxia and hyperthermia.
3. Third phase (20 to 96 hours after exposure), in which full-blown delirium is seen but often fluctuates from moment to moment.
4. Fourth phase, or resolution, characterized by paranoia, deep sleep, reawakening, crawling or climbing automatisms, and eventual reorientation.

Differential diagnosis

The differential diagnosis for irrational and confused patients is a long one and includes anxiety reactions as well as intoxication with a variety of agents, to include hallucinogenic indoles (such as LSD), cannabinoids (such as the delta-9-tetrahydrocannabinol in marijuana), lead, barbiturates, and bromides. All of these conditions can lead to restlessness, lightheadedness (with associated vertigo and ataxia), confusion, and erratic behavior with or without vomiting. Clues that specifically point to BZ or a related compound are the combination of anticholinergic PNS effects ("dry as a bone," "hot as a hare," "red as a beet," and "blind as a bat") with the CNS effects ("mad as a hatter") of slurred and monotonous speech, automatic behavior (perseveration, disrobing, and phantom behaviors (such as "woolgathering"), and vivid, realistic, describable hallucinations (decreasing in size over time) in a patient slipping into and out of delirium.

Signs and symptoms

- Restlessness
- Dizziness or giddiness
- Failure to obey orders
- Confusion
- Erratic behavior
- Stumbling or staggering
- Drymouth (cottonmouth)
- Tachycardia at rest
- Elevated temperature
- Flushing of face
- Blurred vision
- Pupillary dilation
- Slurred or nonsensical speech

- Hallucinations

- Disrobing
- Mumbling
- Stupor and coma.
- Inappropriate smiling or laughter
- Irrational fear
- Distractability
- Difficulty expressing self
- Elevated blood pressure
- Stomach cramps and vomiting
- Euphoric, relaxed, unconcerned attitude
- Hypotension and/or dizziness on sudden standing
- Tremor

- Clinging or pleading
- Seemingly reasonless crying
- Decrease in disturbance with reassurance

Anticholinergics

- Indoles (Schizophrenic psychosis may mimic in some respects.)

Cannabinols

Anxiety reaction

Atropine intoxication from MARK I autoinjector use in a patient not exposed to nerve agents may create similar PNS effects to those seen in BZ intoxication. However, marked confusion from atropine is not normally seen until a total of six or seven autoinjectors have been given (in a hot, dehydrated, or battle-stressed individual, less atropine would probably suffice). Circumstantial evidence may be helpful in this situation. Heat stroke may also generate hot, dry, and confused or stuporous casualties and needs to be considered in the differential diagnosis. Patients with anxiety reactions are usually oriented to time, place, and person but may be trembling, crying, or otherwise panicked. The classic picture of unconcern or "la belle indifférence" may characterize a patient with a conversion reaction, but these patients are also likely to be oriented and lack the anticholinergic PNS signs of BZ poisoning.

Medical management

The admonition to protect oneself first may be difficult when dealing with any intoxication involving a latent period, since initially asymptomatic exposure to health care providers may already have occurred during the same time frame in which patients were exposed. Protection of medical staff from already absorbed and systemically distributed BZ in a patient is not needed.

General supportive management of the patient includes decontamination of skin and clothing (ineffective for already absorbed agent but useful in preventing further absorption of any agent still in contact with the patient), confiscation of weapons and related items from the patient, and observation. Physical restraint may be required in moderately to severely affected patients. The greatest risks to the patient's life are (1) injuries from his or her own erratic behavior (or from the behavior of similarly intoxicated patients) and (2) hyperthermia, especially in patients who are in hot or humid environments or are dehydrated from overexertion or insufficient water intake. A severely exposed patient might be comatose with serious cardiac arrhythmias and electrolyte disturbances. Management of heat stress assumes a high priority in these patients. Because of the prolonged time course in BZ poisoning, consideration should always be given to evacuation to a higher echelon of care.

As a competitive inhibitor of acetylcholine, BZ effectively decreases the amount of acetylcholine "seen" by postsynaptic and postjunctional receptors throughout the body. Specific antidotal therapy in BZ poisoning is therefore geared toward raising the concentration of acetylcholine in these synapses and junctions. Any compound that causes a rise in acetylcholine concentration can potentially overcome BZ-induced inhibition and

restore normal functioning; even the nerve agent VX has been shown to be effective when given under carefully controlled conditions. The specific antidote of choice in BZ poisoning is the carbamate anticholinesterase physostigmine (eserine; Antilirium®), which temporarily raises acetylcholine concentrations by binding reversibly to anticholinesterase on the postsynaptic or postjunctional membrane. Physostigmine is similar in many ways to pyridostigmine and is equally effective when used as a pre-exposure antidotal enhancer ("pretreatment") in individuals at high risk for subsequently encountering soman. However, physostigmine is not used for this purpose because the doses required cause vomiting through CNS mechanisms. In the case of BZ poisoning, a nonpolar compound such as physostigmine is used specifically because penetration into the brain is required in those individuals who already have CNS effects from BZ.

In BZ-intoxicated patients, physostigmine is minimally effective during the first four hours after exposure but is very effective after four hours. Oral dosing generally requires one and a half times the amount of antidote as does IM or IV administration. However, effects from a single intramuscular injection of physostigmine last only about 60 minutes, necessitating frequent re-dosing. It must be emphasized that physostigmine does not shorten the clinical course of BZ poisoning and that relapses will occur if treatment is discontinued prematurely. The temptation to substitute a slow intravenous infusion for intramuscular injections should be tempered by the awareness that IV infusion may lead to nerve-agent-like bradycardia, and too rapid infusion might cause arrhythmias, excessive secretions (to the point of compromising air exchange), and convulsions. Moreover, the sodium bisulfite in commercially available preparations of physostigmine may cause life-threatening allergic responses.

Suggested dosages for physostigmine in the treatment of BZ poisoning follow:

Test dose: If the diagnosis is in doubt, a dose of 1 mg might be given. If a slight improvement occurs, routine dosing should be given.

Routine dosing: Doses of about 45 µg/kg for adults have been recommended. This might be modified by the response. A mental status examination should be done every hour and the dose and time interval of dosing should be modified according to whether the mental status is improved or not. As the patient improves, the dosage requirement will decrease.

Routes of administration:

- IM: 45 µg/kg in adults (20 µg/kg in children)
- IV: 30 µg/kg slowly (1 mg/min)
- PO: 60 µg/kg if patient is cooperative (because of bitter taste, consider diluting in juice)

For each route, titrate about every 60 minutes to mental status.

History and toxicity of physostigmine

The antagonism between physostigmine (the elixir of calabar bean) and atropine (tincture of belladonna) was first reported in 1864 by a physician who successfully treated prisoners who had become delirious after drinking tincture of belladonna. Physicians did not notice this report until the 1950s when atropine coma (in which 50 mg or so of atropine were given to certain psychiatric patients) was successfully treated with physostigmine after

the "therapeutic benefit" had been attained. Again, this went unnoticed until a controlled study, reported in 1967, indicated that anticholinergic intoxication could be successfully, albeit transiently, reversed by physostigmine.

A recent textbook of emergency medicine stated that physostigmine should be used only as "a last resort." It would seem that when a patient needs "last resort" care is the absolute wrong time to administer a potent cholinesterase inhibitor.

The administration of physostigmine by the IV route in a delirious but conscious and otherwise healthy patient is not without peril. It is sometimes difficult to keep a delirious patient quiet long enough to administer the drug (at 1 mg/min is the marketed solution of 1 mg/ml). Even if administered correctly (very slowly), the heart rate may decline from 110 to 45 beat/min over a period of 1 to 2 minutes. The difference in the onset of the effects after IM and IV administration of physostigmine is a matter of only several minutes. Since its use is rarely lifesaving, this slight difference in time of response is inconsequential.

Physostigmine is a safe and effective antidote if used properly. In a conscious and delirious patient it will produce very effective but transient reversal of both the peripheral and central effects of cholinergic blocking compounds. Its use by the IV route is not without hazards. It absolutely should NOT be used in a patient with cardiorespiratory compromise, hypoxia, or acid-base imbalance with a history of seizure disorders or arrhythmias.

Triage

An immediate casualty (possible but unlikely) would be one with cardiorespiratory compromise or severe hyperthermia. Immediate attention to ventilation, hemodynamic status, and temperature control could be lifesaving. Because of its dangers in a hypoxic or hemodynamically challenged patient, physostigmine should be considered a second-line management option to be used only if adequate attention can simultaneously be given to temperature and other vital signs.

The delayed casualty would present with pronounced or worsening anticholinergic signs. Physostigmine should definitely be considered in this kind of patient.

A minimal casualty from a strictly medical standpoint might have mild PNS or CNS anticholinergic effects. Given the time course of BZ intoxication, however, these patients should not be considered able to manage themselves or capable of routine return to duty and should be relieved of their weapons, observed, and, if the holding capacity at the current echelon is exceeded, evacuated.

An expectant casualty (also possible but unlikely) would have severe cardiorespiratory compromise in a situation in which treatment or evacuation resources are too limited to allow the necessary attention to be directed to him or her.

Return to duty

Given the time course of the intoxication, early return to duty is probably not a realistic possibility for the majority of casualties who may require observation and management for several days at the least.

Atropine

Systematic (IUPAC) name

(8-methyl-8-azabicyclo[3.2.1]oct-3-yl) 3-hydroxy-2-phenyl-propanoate

Identifiers

CAS number 51-55-8

ATC code A03**BA01** S01**FA01**

PubChem 174174

DrugBank APRD00807

Chemical data

Formula $C_{17}H_{23}NO_3$

Mol. weight 289.369

Pharmacokinetic data

Bioavailability **25%**

Metabolism 50% hydrolysed to tropine and tropic acid

Half life 2 hours

Excretion 50% excreted unchanged in urine

Therapeutic considerations

Routes oral, i.v., rectal

Atropine is a tropane alkaloid extracted from the deadly nightshade (Atropa belladonna) and other plants of the family Solanaceae. It is a secondary metabolite of these plants and serves as a drug with a wide variety of effects. Being potentially deadly, it derives its name from Atropos, one of the three Fates who, according to Greek mythology, chose how a person was to die.

Physiological effects and uses

Generally, atropine lowers the "rest and digest" activity of all muscles and glands regulated by the parasympathetic nervous system. This occurs because atropine is a competitive antagonist of the muscarinic acetylcholine receptors. (Acetylcholine is the main

neurotransmitter used by the parasympathetic nervous system.) Therefore, it may cause swallowing difficulties and reduced secretions.

Ophthalmic use

Topical atropine is used as a cycloplegic, to temporarily paralyze the accommodation reflex, and as a mydriatic, to dilate the pupils. Atropine degrades slowly, typically wearing off in 2 to 3 days, so tropicamide and phenylephrine is generally preferred as a mydriatic. In atropine-induced mydriasis, the mechanism of action involves blocking the contraction of the circular pupillary sphincter muscle which is normally stimulated by acetylcholine release, thereby allowing the radial pupillary dilator muscle to contract and dilate the pupil. Atropine is contraindicated in patients predisposed to narrow angle glaucoma.

Resuscitation

Injections of atropine are used in the treatment of bradycardia (an extremely low heart rate), asystole and pulseless electrical activity (PEA) in cardiac arrest. This works because the main action of the vagus nerve of the parasympathetic system on the heart is to slow it down. Atropine blocks that action and therefore may speed up the heart rate.

Atropine is also useful in treating first degree heart block, second degree heart block Type 1 Wenckebach, and also third degree heart block with a high Purkinje or AV-nodal escape rhythm. It is contraindicated in second degree heart block Type II Mobitz, and in third degree heart block with a low Purkinje or ventricular escape rhythm.

The main action of the parasympathetic nervous system is to stimulate the M2 muscarinic receptor in the heart, but atropine inhibits this action.

Secretions and bronchoconstriction

Atropine's actions on the parasympathetic nervous system inhibits salivary, sweat, and mucus glands. This can be useful in treating Hyperhidrosis and can prevent the death rattle of dying patients. Even though it has not been officially indicated for either of these purposes by the FDA, it has been used by physicians for these purposes.

Antidote for organophosphate poisoning

By blocking the action of acetylcholine at muscarinic receptors, atropine also serves as an antidote for poisoning by organophosphate insecticides and nerve gases. Troops who are likely to be attacked with chemical weapons often carry autoinjectors with atropine and obidoxime which can be quickly injected into the thigh. It is often used in conjunction with Pralidoxime chloride.

Some of the nerve gases attack and destroy acetylcholinesterase, so the action of acetylcholine becomes prolonged. Therefore, atropine can be used to reduce the effect of acetylcholine.

Side effects and overdoses

Adverse reactions to atropine include ventricular fibrillation, supraventricular or ventricular tachycardia, giddiness, nausea, blurred vision, loss of balance, dilated pupils, photophobia, and possibly, notably in the elderly, confusion, hallucinations, and excitation. These latter effects are due to the fact that atropine is able to cross the blood-brain barrier. Because of the hallucinogenic properties, some have used the drug recreationally, though this is very dangerous and often unpleasant.

In overdoses, atropine is poisonous. Atropine is sometimes added to other potentially addictive drugs; abuse of those drugs is then prevented by the unpleasant effects of atropine overdose.

Atropine can cause heart rate slowing when given at very low doses, presumably as a result of a weak partial agonist effect at the cardiac muscarinic receptors.

The antidote to atropine is physostigmine or pilocarpine.

Chemistry and pharmacology

Atropine is a racemic mixture of D-hyoscyamine and L-hyoscyamine, with most of its physiological effects due to L-hyoscyamine. Its pharmacological effects are due to binding to muscarinic acetylcholine receptors.

The most common atropine compound used in medicine is atropine sulfate (C17H23NO3)2. H2SO4. H2O, the full chemical name is 1± H, 5± H-Tropan-3-± ol (±)-tropate(ester), sulfate monohydrate.

History

Atropine extracts from the Egyptian henbane were used by Cleopatra in the last century B.C. to dilate her pupils, in the hope that she would appear more alluring.

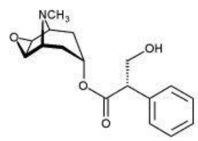
In the Renaissance, women used the juice of the berries of Atropa belladonna to enlarge the pupils of their eyes, for cosmetic reasons; "bella donna" is Italian for "beautiful lady".

Atropine and its mydriatic effects were discovered in 1833 by the German chemist Friedrich Ferdinand Runge (1795-1867).

Natural sources

Atropine is found in many members of the Solanaceae family. The most commonly found sources are Atropa belladonna, Datura inoxia, D. metel, and D. stramonium. Other sources include members of the Brugmansia and Hyoscyamus genera. The Nicotiana genus (including the tobacco plant, N. tabacum) is also found in the Solanaceae family, but these plants do not contain atropine or other tropane alkaloids.

Scopolamine



Systematic (IUPAC) name

(-)-(1S,3S,5R,6R,7S,8S)- 6,7-epoxy-3-[(S)-tropoyloxy]tropane

Identifiers

CAS number 138-12-5

ATC code A04**AD01** N05**CM05**, S01**FA02**

PubChem 5184

DrugBank APRD00616

Chemical data

Formula C***17***H***21***NO***4***

Mol. weight 303.353 g/mol

Therapeutic considerations

Pregnancy cat. $C_{(US)}$

Legal status $_{\text{-only(US)}}$

Routes transdermal, ocular, (formerly oral, subcutaneous)

Scopolamine, also known as *hyoscine*, is a tropane alkaloid drug obtained from plants of the family Solanaceae (nightshades), such as henbane or jimson weed (Datura species). It is part of the secondary metabolites of plants.

It acts as a competitive antagonist at muscarinic acetylcholine receptors; it is thus classified as an anticholinergic.

In medicine, it is usually used in the form scopolamine hydrobromide. It can be used as a depressant of the central nervous system, though it can cause delirium in the presence of pain, mydriasis (pupillary dilation), and cycloplegia (paralysis of the eye muscles). When combined with morphine, it produces a tranquilized state known as twilight sleep and amnesia. Although originally used in obstetrics, it is now considered dangerous for that purpose. Sometimes side effects of scopolamine can be mistaken for symptoms of cancer

because of the nausea and anisocoria associated with brain tumors. However, scopolamine induced anisocoria clears up usually within 3 days.

It is used in ophthalmology to deliberately cause cycloplegia and mydriasis so that certain diagnostic procedures may be performed. It is also used in the treatment of iridocyclitis.

In otolaryngology it has been used to ease the trauma of intubation.

It is also an antiemetic (prevents vomiting), antivertigo (prevents dizziness), and antispasmodic (reduces smooth muscle contractions; although a derivate called butylscopolamine, that does not cross the blood-brain barrier, is used preferably). It can be used as a pre-anesthetic sedation, as an antiarrhythmic (preventing irregular heartbeat) during anesthesia, and for the prevention of motion sickness. Transdermal patches, (Scopoderm TTS patches), are available for the prevention of symptoms of travel sickness.

The drug is highly toxic and has to be used in minute doses. An overdose can cause delirium, delusions, paralysis, stupor and death.

The use of scopolamine as a truth drug was investigated by various intelligence agencies, including the CIA, during the 1950s. see: Project MKULTRA. It was found that, due to the hallucinogenic side effects of the drug, the truth was prone to distortion, and the project was subsequently abandoned.. Nazi doctor Josef Mengele experimented on scopolamine as an interrogation drug.

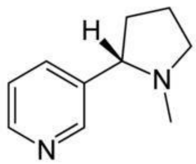
Scopolamine is used criminally as a date rape drug and as an aid to robbery, the most common act being the clandestine drugging of a victim's drink. It is preferred because it induces retrograde amnesia, or an inability to recall events prior to its administration. Victims of this crime are often admitted to a hospital in police custody, under the assumption that the patient is experiencing a psychotic episode. A telltale sign is a fever accompanied by a lack of sweat.

In Colombia a plant admixture containing scopolamine called Burundanga has been used shamanically for decades. In recent years its criminal use (as outlined above) has become an epidemic. Approximately fifty percent of emergency room admissions for poisoning in Bogotá have been attributed to scopolamine. Also in Caracas, Venezuela, crime related to burundanga techniques has multiplied in the last years.

Due to its effectiveness against sea-sickness it has become commonly used by scuba divers. However, this has led to the discovery of another side effect. In deep water, below 50–60 feet, some divers have reported pain in the eyes, but the pain subsides quickly if the diver ascends to a depth of 40 feet or less. Mydriatics can precipitate an attack of glaucoma in susceptible patients, so the medication should be used with extra caution among divers who intend to go below 50 feet.

In popular culture, scopolamine has achieved a moderate level of notoriety via its mention in the film I Was a Teenage Werewolf, where Dr. Alfred Brandon uses it as part of his endeavor to regress the titular character to his "primitive roots." According to one internet reviewer (http://twtd.bluemountains.net.au/Rick/liz_tw.htm), "Prepare the scopolamine" is the only scientifically accurate line in the entire film.

Nicotinic antagonists



Nicotine

Nicotinic acetylcholine receptors, or *nAChRs*, are ionotropic receptors that form ion channels in cells' plasma membranes. Like the other type of acetylcholine receptors, muscarinic acetylcholine receptors, their opening is triggered by the neurotransmitter acetylcholine, but they are also opened by nicotine (Siegel et al., 1999; Itier and Bertrand, 2001). Their action is inhibited by curare.

Nicotinic acetylcholine receptors are present in many tissues in the body. The neuronal receptors are found in the central nervous system and the peripheral nervous system. The neuromuscular receptors are found in the neuromuscular junctions of somatic muscles; stimulation of these receptors causes muscular contraction.

Structure

Nicotinic receptors, with a molecular weight of about 280 kDa, are made up of five receptor subunits, arranged symmetrically around the central pore. They share similarities with GABAA receptors, glycine receptors, and the type 3 serotonin receptors, which are all therefore classed into the nicotinicoid receptor family, or the signature Cys-loop proteins (Cascio, 2004).

Twelve types of nicotinic receptor subunits, ±2 through 10 and ^{2}2 through 4 (Itier and Bertrand, 2001), combine to form pentamers. The subunits are somewhat similar to one another, especially in the hydrophobic regions (Siegel et al., 1999). The muscle form of the nAChR consist of two ± subunits, a ^{2}, a ´ and either a ^{3} or an µ (Siegel et al., 1999; Itier and Bertrand, 2001; Giniatullin et al., 2005). The neuronal forms are much more heterogeneous, with a wide range of possible subunit combinations.

The sites for binding ACh are on the outside of the ± subunits near their N termini (Siegel et al., 1999). When the agonist binds, the ± subunits become more similar to the other subunits, the channel becomes more symmetrical (Colquhoun and Sivilotti, 2004), and a pore with a diameter of about 0.65 nm opens (Siegel et al., 1999).

Opening the channel

Nicotinic AChRs may exist in different interconvertible conformational states. Binding of nicotine stabilizes the open and desensitised states. Opening of the channel allows positively charged ions, in particular, sodium and calcium, to enter the cell.

The nAChR is permeable to Na± and K±, with some subunit combinations that are also permeable to Ca2+ (Siegel et al., 1999). The amount of sodium and potassium the channels allow through their pores (their conductance) is about 25 pS (Siegel et al., 1999), but the conductance depends on the actual subunit composition. Interestingly, because some

neuronal nAChRs are permeable to Ca2+, they can affect the release of other neurotransmitters (Itier and Bertrand, 2001). The channel usually opens rapidly and tends to remain open until the agonist diffuses away, usually for about 1 millisecond (Siegel et al., 1999). However, AChRs can open sometimes with only one agonist bound and in rare cases with no agonist bound, and they can close spontaneously even when ACh is bound, so ACh binding only creates a probability of pore opening, which increases as more ACh binds (Colquhoun and Sivilotti, 2004).

Effects

This activation of receptors by nicotine modifies the state of neurons through two main mechanisms. On one hand, the movements of cations cause a depolarization of the plasma membrane, which results in an excitation, particularly of neurons, but also by the activation of other voltage-gated ion channels. On the other hand, the entry of calcium acts, either directly or indirectly, on different intracellular cascades leading, for example, to the regulation of the activity of some genes or the release of neurotransmitters.

Roles

The subunits of the nicotinic receptors belong to a multigene family (16 members in human) and the assembly of combinations of subunits results in a large number of different receptors (For more information see the Ligand Gated Ion Channel database). These receptors, with highly variable kinetic, electrophysiological and pharmacological properties, respond differently to nicotine, at very different effective concentrations. This functional diversity allows them to take part in two major types of neurotransmission. Classical synaptic transmission (wiring transmission) involves the release of high concentrations of neurotransmitter, acting on immediately neighbouring receptors. In contrast, paracrine transmission (volume transmission) involves neurotransmitters released by synaptic buttons or varicosities, which then diffuse through the extra-cellular medium until they reach their receptors, which may be distant. Nicotinic receptors can also be found in different synaptic locations, for example the muscle nicotinic receptor always functions post-synaptically. The neuronal forms of the receptor can be found both post-synaptically (involved in classical neurotransmission) and pre-synaptically (where they can influence the release of other neurotranmsitters).

Subunits

To date 17 nAChR subunits have been identified, these are divided into muscle-type and neuronal-type subunits. Of these 17 subunits, ±2-±7 and ^{2}2-^{2}4 have been cloned in humans, the remaining genes identified in chick and rat genomes (Graham et al. 2002). The nAChR subunits have been divided into 4 subfamilies (I-IV) based on similarities in protein sequence. In addition, subfamily III has been further divided into 3 tribes.

Neuronal-type					Muscle-type
I	II	III			IV
		1	2	3	
α9, α10	α7, α8	α2, α3, α4, α6	β2, β4	β3, α5	α1, β1, δ, γ, ε

- *Alpha genes:* CHRNA1 *(muscle),* CHRNA2 *(neuronal),* CHRNA3, CHRNA4, CHRNA5, CHRNA6, CHRNA7, CHRNA8, CHRNA9, CHRNA10
  - Beta genes: CHRNB1 (muscle), CHRNB2 (neuronal), CHRNB3, CHRNB4,
  - Other genes: CHRND (delta), CHRNE (epsilon), CHRNG (gamma)

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Tobacco

Nicotiana tabacum

Scientific classification

Kingdom: Plantae

Class: Magnoliopsida

Order: Solanales

Family: Solanaceae

Genus: **Nicotiana**

Species

Nicotiana acuminata
Nicotiana alata
Nicotiana attenuata
Nicotiana benthamiana
Nicotiana clevelandii
Nicotiana excelsior
Nicotiana forgetiana
Nicotiana glauca
Nicotiana glutinosa
Nicotiana langsdorffii
Nicotiana longiflora
Nicotiana obtusifolia
Nicotiana paniculata
Nicotiana plumbagifolia
Nicotiana quadrivalvis
Nicotiana repanda
Nicotiana rustica
Nicotianasuaveolens
Nicotiana sylvestris
Nicotiana tabacum
Nicotiana tomentosa

Ref: ITIS 30562

as of August 26, 2005

Tobacco (Nicotiana spp., L.)refers to a genus of broad-leafed plants of the nightshade family indigenous to North and South America, or to the dried and cured leaves of such plants. Tobacco leaves are often smoked (see tobacco smoking) in the form of a cigar or cigarette, or in a smoking pipe, or in a water pipe or a hookah. This can damage the lungs and can also potentially cause lung disorders such as asthma. Tobacco is also chewed, "dipped" (placed between the cheek and gum), and sniffed into the nose as finely powdered snuff.

Tobacco contains nicotine, a powerful neurotoxin that is particularly harmful to insects. All means of consuming tobacco result in the absorption of nicotine in varying amounts into the user's bloodstream, and over time the development of tolerance and dependence. Absorption quantity, frequency and speed seem to have a direct relationship with how strong a dependence and tolerance, if any, might be created. A lethal dose of nicotine is contained in as little as one half of a cigar or three cigarettes; however, only a small fraction of the nicotine contained in these products is actually released into the smoke, and most clinically significant cases of nicotine poisoning are the result of concentrated forms of the compound used as insecticides. Other active alkaloids in tobacco include harmala alkaloids.

Tobacco smoking carries significant risks including the potential to develop various cancers as well as strokes, and severe cardiovascular and respiratory diseases. [1] Significantly shorter life expectancies have been associated with tobacco smoking. [2] Many jurisdictions have enacted smoking bans in an effort to minimize possible damage to public health caused by tobacco smoking. The substantially increased risk of developing cancer as a result of tobacco usage seems to be due to the plethora of nitrosamines and other carcinogenic compounds found in tobacco and its residue as a result of anaerobic heating, either due to smoking or to flue-curing or fire-curing. The use of flue-cured or fire-cured smokeless tobacco in lieu of smoked tobacco reduces the risk of respiratory cancers but still carries significant risk of oral cancer. [3] In contrast, use of steam-cured chewing tobacco (snus), avoids the carcinogenicity by not generating nitrosamines, but the negative effects of the nicotine on the cardiovascular system and pancreas are not ameliorated.[4]

History

Native Americans used tobacco before Europeans arrived in North & South America, and early European settlers in North & South America learned to smoke and brought the practice back to Europe, where it became hugely popular. At extremely high doses, tobacco becomes hallucinogenic; accordingly, Native Americans generally did not use the drug recreationally. Rather, it was often consumed in extraordinarily high quantities and used as an entheogen; generally, this was done only by experienced shamans or medicine men. In addition to being smoked, uncured tobacco was often eaten, drunk as tobacco juice, or used in enemas. Early missionaries often reported on the state caused by tobacco, but as it spread into the west, it was no longer used in such large quantities or for entheogenic purposes. Religious use of tobacco is still common among many indigenous peoples, particularly those of South America.

With the arrival of Europeans, tobacco became one of the primary products fueling the colonization of the future American South, long before the creation of the United States. The

initial colonial expansion, fueled by the desire to increase tobacco production, was one cause of the first colonial conflicts with Native Americans and became a driving factor for the use of African slaves' labor.

In 1609, John Rolfe arrived at the Jamestown Settlement in Virginia. He is credited as the first man to successfully raise tobacco for commercial use at Jamestown. The tobacco raised in Virginia at that time, Nicotiana rustica, was not to the liking of the Europeans, but Rolfe had brought some seed for Nicotiana tabacum with him from Bermuda. Shortly after arriving, his first wife died, and he married Pocahontas, a daughter of Chief Powhatan. Although most of the settlers wouldn't touch the tobacco crop, Rolfe was able to make his fortune farming it for export at Varina Farms Plantation. When he left for England with Pocahontas, he was wealthy. When Rolfe returned to Jamestown following Pocahontas's death in England, he continued to improve the quality of tobacco. By 1620, 40,000 pounds of tobacco were shipped to England. By the time John Rolfe died in 1622, Jamestown was thriving as a producer of tobacco and Jamestown's population would top 4,000. Tobacco led to the importation of the colony's first black slaves as well as women from England in 1619.

The importation of tobacco into Europe was not without resistance and controversy, even in the 17th century. King James I of England (James VI of Scotland) wrote a famous polemic titled A Counterblaste to Tobacco in 1604 (published in 1672). In his essay, the king denounced tobacco use as "[a] custome lothsome to the eye, hatefull to the Nose, harmefull to the braine, dangerous to the Lungs, and in the blacke stinking fume thereof, neerest resembling the horrible Stigian smoke of the pit that is bottomelesse." In that same year, an English statute was enacted that placed a heavy protective tariff on every pound of tobacco brought into England.

Throughout the 17th and 18th centuries, tobacco continued to be the "cash crop" of the Virginia Colony, along with The Carolinas. Large tobacco warehouses filled the areas near the wharfs of new thriving towns such as Richmond and Manchester at the fall line (head of navigation) on the James River, and Petersburg on the Appomattox River.

Until 1883, tobacco excise tax accounted for one third of internal revenue collected by the United States government.

A historian of the American South in the late 1860s reported on typical usage in the region where it was grown: [1]

The chewing of tobacco was well-nigh universal. This habit had been widespread among the agricultural population of America both North and South before the war. Soldiers had found the quid a solace in the field and continued to revolve it in their mouths upon returning to their homes. Out of doors where his life was principally led the chewer spat upon his lands without offence to other men, and his homes and public buildings were supplied with spittoons. Brown and yellow parabolas were projected to right and left toward these receivers, but very often without the careful aim which made for cleanly living. Even the pews of fashionable churches were likely to contain these familiar conveniences. The large numbers of Southern men, and these were of the better class (officers in the Confederate army and planters, worth $20,000 or more, and barred from general amnesty) who presented themselves for the pardon of President Johnson, while they sat awaiting his pleasure in the ante-room at the White House, covered its floor with pools and rivulets of their spittle. An observant traveller in the South in 1865 said that in his belief seven-tenths of all persons above the age of twelve years, both male and female, used tobacco in some

form. Women could be seen at the doors of their cabins in their bare feet, in their dirty one-piece cotton garments, their chairs tipped back, smoking pipes made of corn cobs into which were fitted reed stems or goose quills. Boys of eight or nine years of age and half-grown girls smoked. Women and girls "dipped" in their houses, on their porches, in the public parlors of hotels and in the streets.

As a lucrative crop, tobacco has been the subject of a great deal of biological and genetic research. The economic impact of Tobacco Mosaic disease was the impetus that led to the isolation of Tobacco mosaic virus, the first virus to be identified; the fortunate coincidence that it is one of the simplest virii and can self-assemble from purified nucleic acid and protein led in turn to the rapid advancement of the field of virology. The 1946 Nobel Prize in Chemistry was shared by Wendell Meredith Stanley for his 1935 work crystallizing the virus, and showing that it still remains active.

Etymology

The Spanish word "tabaco" is thought to have its origin in Arawakan language, particularly, in the Taino language of the Caribbean, said to refer to a roll of these leaves (according to Bartolome de Las Casas, 1552) or to the "tabago", a kind of y-shaped pipe for sniffing tobacco smoke (according to Oviedo, the leaves themselves were referred to as Cohiba, but Sp. tabaco (also It. tobacco) was commonly used to define medicinal herbs from 1410, originating from the Arabic "tabbaq", reportedly since the 9th century, as the name of various herbs. The word might then be European, and later applied to this plant from the Americas.

Cultivation

Top Ten Tobacco Producers - 2005 (million metric ton)

China 2.51

Brazil 0.88

India 0.60

United States 0.29

Indonesia 0.14

Turkey 0.14

Greece 0.12

Argentina 0.12

Italy 0.11

Pakistan 0.08

World Total 6.38

Source: UN Food & Agriculture Organisation (FAO)[5]

Sowing

Tobacco seeds are scattered onto the surface of the soil, as their germination is activated by light. In colonial Virginia, seedbeds were fertilized with wood ash or animal manure (frequently powdered horse manure). Seedbeds were then covered with branches to protect the young plants from frost damage. These plants were left to grow until around April.

In the nineteenth century, young plants came under increasing attack from the flea beetle (Epitrix cucumeris or Epitrix pubescens), causing destruction of half the United States tobacco crop in 1876. In the years afterward, many experiments were attempted and discussed to control the flea beetle. By 1880 it was discovered that replacing the branches with a frame covered by thin fabric would effectively protect plants from the beetle. This practice spread until it became ubiquitous in the 1890s.

Today, in the United States, unlike other countries, tobacco is often fertilized with the mineral apatite in order to partially starve the plant for nitrogen, which changes the taste. This (together with the use of licorice and other additives) accounts for the different flavor of American cigarettes from those available in other countries. There is, however, some suggestion that this may have adverse health effects attributable to the polonium content of apatite.

Transplanting

After the plants have reached a certain height, they are transplanted into fields. This was originally done by making a relatively large hole in the tilled earth with a tobacco peg, then placing the small plant in the hole. Various mechanical tobacco planters were invented throughout the late 19th and early 20th century to automate this process, making a hole, fertilizing it, and guiding a plant into the hole with one motion.

Harvest

Tobacco is harvested in one of two ways. In the oldest method, the entire plant is harvested at once by cutting off the stalk at the ground with a curved knife. In the nineteenth century, bright tobacco began to be harvested by pulling individual leaves off the stalk as they ripened. The leaves ripen from the ground upwards, so a field of tobacco may go through several "pullings" before the tobacco is entirely harvested, and the stalks may be turned into the soil. "Cropping" or "pulling" are terms for pulling leaves off tobacco. Leaves are cropped as they ripen, from the bottom of the stalk up. The first crop at the very bottom of the stalks are called "sand lugs", as they are often against the ground and are coated with dirt splashed up when it rains. Sand lugs weigh the most, and are most difficult to work with. Originally

workers cropped the tobacco and placed it on mule-pulled sleds. Eventually tractors with wagons were used to transport leaves to the stringer, an apparatus which uses twine to sew leaves onto a stick .

Some farmers use "tobacco harvesters" - basically a trailer pulled behind a tractor. The harvester is a wheeled sled or trailer that has seats for the croppers to sit on and seats just in front of these for the "stringers" to sit on. The croppers pull the leaves off in handfuls, and pass these to the "stringer", who loops twine around the handfuls of tobacco and hangs them on a long wooden square pole. Traditionally, the croppers, down in the dark and wet, with their faces getting slapped by the huge tobacco leaves, were men, and the stringers seated on the higher elevated seats were women. The harvester has places for 4 teams of workers: 8 people cropping and stringing, plus a packer who takes the heavy strung poles of wet green tobacco from the stringers and packs them onto the pallet section of the harvester, plus a driver, making the total crew of each harvester 10 people. Interestingly, the outer seats are suspended from the harvester - slung out over to fit into the aisles of tobacco. As these seats are suspended it is important to balance the weight of the 2 outside teams (similar to a playground see-saw). Having too heavy or light a person in an unbalanced combination often results in the harvester tipping over especially when turning around at the end of a lane. Water tanks are a common feature on the harvester due to heat, and danger of dehydration for the workers. Salt tablets sometimes get used as well.

Pests

Pests of tobacco include the moths Endoclita excrescens, Manduca sexta (the Tobacco hornworm), and Manduca quinquemaculata. Other Lepidoptera whose larvae use tobacco as a food plant include Angle Shades, Cabbage Moth, Mouse Moth, Nutmeg Moth, Setaceous Hebrew Character and Turnip Moth. The dry tobacco leaves and cigarettes are sometimes used as food for the Cigarette Beetle (Lasioderma serricorne).

Curing

Cut plants or pulled leaves are immediately transferred to tobacco barns (kiln houses), where they will be cured. Curing methods varies with the type of tobacco grown, and tobacco barn design varies accordingly. Air-cured tobacco is hung in well-ventilated barns and allowed to dry over a period of weeks. Fire-cured tobacco is hung in large barns where smoldering fires of hardwoods are kept burning. Flue-cured tobacco was originally strung onto tobacco sticks, which were hung from tier-poles in curing barns (Aus: kilns, also traditionally called Oasts). These barns have flues which run from externally-fed fire boxes, heat-curing the tobacco without exposing it to smoke. Traditional curing barns in the U.S. are falling into disuse, as the trend toward more efficient prefabricated metal "bulk bars", allows greater efficiency. Curing and subsequent aging allows for the slow oxidation and degradation of carotenoids in tobacco leaf. This produces certain compounds in the tobacco leaves very similar and give a sweet hay, tea, rose oil, or fruity aromatic flavor that contribute to the "smoothness" of the smoke. Starch is converted to sugar which glycates protein and is oxidized into advanced glycation endproducts (AGEs), a caramelization process that also

adds flavor. Inhalation of these AGEs in tobacco smoke contributes to atherosclerosis and cancer[2].

Unaged or low quality tobacco is often flavoured with these naturally occurring compounds. Tobacco flavoring is a significant part of a multi-million dollar industry.

The aging process continues for a period of months and often extends into the post-curing process.

Post-cure processing

After tobacco is cured, it is moved from the curing barn into a storage area for processing. If whole plants were cut, the leaves are removed from the tobacco stalks in a process called stripping. For both cut and pulled tobacco, the leaves are then sorted into different grades. In colonial times, the tobacco was then "prized" into hogsheads for transportation. In bright tobacco regions, prizing was replaced by stacking wrapped "hands" into loose piles to be sold at auction. Today, most cured tobacco is baled before sales under contract.

Other Types

Aromatic Fire-cured

Aromatic Fire-cured smoking tobacco is a robust variety of tobacco used as a condimental for pipe blends. It is cured by smoking over gentle fires. In the United States, it is grown in the western part of Tennessee, Western Kentucky and in Virginia. Latakia is produced from oriental varieties of N. tabacum. The leaves are cured and smoked over smoldering fires of local hardwoods and aromatic shrubs in Cyprus and Syria. Latakia has a pronounced flavor and a very distinctive aroma, and is used in the so-called Balkan and English-style pipe tobacco blends.

Fire-cured tobacco grown in Kentucky and Tennessee is used in some chewing tobaccos, moist snuff, some cigarettes and as a condiment leaf in pipe tobacco blends. It has a rich, slightly floral taste, and adds body and aroma to the blend.

Brightleaf tobacco

Prior to the American Civil War, the tobacco grown in the US was almost entirely fire-cured dark-leaf. This was planted in fertile lowlands, used a robust variety of leaf, and was fire cured or air cured.

Sometime after the War of 1812, demand for a milder, lighter, more aromatic tobacco arose. Ohio and Maryland both innovated quite a bit with milder varieties of the tobacco plant. Farmers around the country experimented with different curing processes. But the breakthrough didn't come until 1854.

It had been noticed for centuries that sandy, highland soil produced thinner, weaker plants. Captain Abisha Slade, of Caswell County, North Carolina had a good deal of infertile, sandy soil, and planted the new "gold-leaf" varieties on it. Slade owned a slave, Stephen, who accidentally produced the first real bright tobacco. He used charcoal to restart a fire used to

cure the crop. The surge of heat turned the leaves yellow. Using that discovery, Slade developed a system for producing bright tobacco, cultivating on poorer soils and using charcoal for heat-curing.

News spread through the area pretty quickly. The worthless sandy soil of the Appalachian piedmont was suddenly profitable, and people rapidly developed flue-curing techniques, a more efficient way of smoke-free curing. By the outbreak of the War, the town of Danville, Virginia actually had developed a bright-leaf market for the surrounding area in Caswell County, North Carolina and Pittsylvania County, Virginia.

Danville was also the main railway head for Confederate soldiers going to the front. These brought bright tobacco with them from Danville to the lines, traded it with each other and Union soldiers, and developed quite a taste for it. At the end of the war, the soldiers went home and suddenly there was a national market for the local crop. Caswell and Pittsylvania counties were the only two counties in the South that experienced an increase in total wealth after the war.

White burley

In 1864, George Webb of Brown County, Ohio planted Red Burley seeds he had purchased, and found that a few of the seedlings had a whitish, sickly look. He transplanted them to the fields anyway, where they grew into mature plants but retained their light color. The cured leaves had an exceedingly fine texture and were exhibited as a curiosity at the market in Cincinnati. The following year he planted ten acres (40,000 m^2) from seeds from those plants, which brought a premium at auction. The air-cured leaf was found to be mild tasting and more absorbent than any other variety. White Burley, as it was later called, became the main component in chewing tobacco, American blend pipe tobacco, and American-style cigarettes. The white part of the name is seldom used today, since red burley, a dark air-cured variety of the mid-1800s, no longer exists.

Shade tobacco

It is not well known that the northern US state of Connecticut is also one of the important tobacco-growing regions of the country. Long before Europeans arrived in the area, Native Americans harvested wild tobacco plants that grew along the banks of the Connecticut River. Today, the Connecticut River valley north of Hartford, Connecticut is known as Tobacco Valley, and the fields and drying sheds are visible to travelers on the road to and from Bradley Field, the major Connecticut airport. The tobacco grown here is known as shade tobacco, and is used as outer wrappers for some of the world's finest cigars.

Early Connecticut colonists acquired from the Native Americans the habit of smoking tobacco in pipes and began cultivating the plant commercially, even though the Puritans referred to it as the "evil weed". The plant was outlawed in Connecticut in 1650, but in the 1800s as cigar smoking began to be popular, tobacco farming became a major industry, employing farmers, laborers, local youths, southern African Americans, and migrant workers.

Working conditions varied from pleasant summer work for students, to backbreaking exploitation of migrants. Each tobacco plant yields only 18 leaves useful as cigar wrappers, and each leaf requires a great deal of individual manual attention after harvesting, some of which must be carried out in the drying sheds, where the temperature exceeds 100 degrees Fahrenheit.

In 1921, Connecticut tobacco production peaked, at 31,000 acres (125 km^2) under cultivation. The rise of cigarette smoking and the decline of cigar smoking has caused a corresponding decline in the demand for shade tobacco, reaching a minimum in 1992 of 2,000 acres (8 km^2) under cultivation. Since then, however, cigar smoking has become more popular again, and in 1997 tobacco farming had risen to 4,000 acres (16 km^2). The industry has weathered some major catastrophes, including a devastating hailstorm in 1929, and an epidemic of brown spot fungus in 2000.

Perique

Perhaps the most strongly-flavored of all tobaccos is the Perique, from Saint James Parish, Louisiana. When the Acadians made their way into this region in 1755, the Choctaw and Chickasaw tribes were cultivating a variety of tobacco with a distinctive flavor. A farmer called Pierre Chenet is credited with first turning this local tobacco into the Perique in 1824 through the technique of pressure-fermentation.

The tobacco plants are manually kept suckerless, and pruned to exactly 12 leaves, through their early growth. In late June, when the leaves are a dark, rich green and the plants are 24-30 inches (600 to 750 mm) tall, the whole plant is harvested in the late evening and hung to dry in a sideless curing barn. Once the leaves have partially dried, but while still supple (usually less than 2 weeks in the barn), any remaining dirt is removed and the leaves are moistened with water and stemmed by hand. The leaves are then rolled into "torquettes" of approximately 1 pound (450 g) and packed into hickory whiskey barrels. The tobacco is then kept under pressure using oak blocks and massive screw jacks, forcing nearly all the air out of the still-moist leaves. Approximately once a month, the pressure is released, and each of the torquettes is "worked" by hand to permit a little air back into the tobacco. After a year of this treatment, the Perique is ready for consumption, although it may be kept fresh under pressure for many years. Extended exposure to air degrades the particular character of the Perique. The finished tobacco is dark brown, nearly black, very moist with a fruity, slightly vinegary aroma.

Considered the truffle of pipe tobaccos, the Perique is used as a component of many blended pipe tobaccos, but is too strong to be smoked pure. At one time, the freshly moist Perique was also chewed, but none is now sold for this purpose. Less than 16 acres (65,000 m^2) of this crop remain in cultivation, most by a single farmer called Percy Martin, in Grande Pointe, Louisiana. For reasons unknown, the particular flavor and character of the Perique can only be acquired on a small triangle of Saint James Parish, less than 3 by 10 miles (5 by 16 km). Although at its peak, Saint James Parish was producing around 20 tons of the Perique a year, output is now merely a few barrelsful.

It is traditionally a pipe tobacco, and is still very popular with pipe-smokers, typically blended with pure Virginia to lend spice, strength, and coolness to the blend. Perique may

now also be found in the Perique cigarettes of Santa Fe Natural Tobacco Co., in an approximately 1 part to 5 blend with lighter tobaccos. A similar tobacco, based on pressure-fermented Kentucky tobacco is available by the name Acadian Green River Perique.

Oriental Tobacco

Oriental tobacco is a sun-cured, highly aromatic, small-leafed variety that is grown in Turkey, Greece, Bulgaria, and Macedonia. Oriental tobacco is frequently referred to as "Turkish tobacco", as these regions were all historically part of the Ottoman Empire. Many of the early brands of cigarettes were made mostly or entirely of Oriental tobacco; today, its main use is in blends of pipe and especially cigarette tobacco (a typical American cigarette is a blend of bright Virginia, burley and Oriental).

Tobacco products

Snuff

Snuff is a generic term for fine-ground smokeless tobacco products. Originally the term referred only to dry snuff, a fine tan dust popular mainly in the eighteenth century. This is often called "Scotch Snuff", a folk-etymology derivation of the scorching process used to dry the cured tobacco by the factory.

European (dry) snuff is intended to be sniffed up the nose. Snuff is not "snorted" due to the fact that snuff shouldn't get past the nose i.e.; into sinuses, throat or lungs. European snuff comes in several varieties: Plain, Toast (fine ground - very dry), "Medicated" (menthol, camphor, eucalyptus, etc.), Scented and Schmalzler (a German variety.) The major brand names of European snuff are: Bernards (Germany), Fribourg & Treyer (UK), Gawith (UK), Gawith Hoggarth (UK), Hedges (UK), Lotzbeck (Germany), McChrystal's (UK), Pöschl (Germany) and Wilsons of Sharrow (UK).

Snuff has even been found to be beneficial in some cases of hay fever due to the fact that the snuff may prevent allergens from getting to the mucus membrane within the nose. *American* snuff is much stronger, and is intended to be dipped. It comes in two varieties -- "sweet" and "salty". Until the early 20th century, snuff dipping was popular in the United States among rural people, who would often use sweet barkless twigs to apply it to their gums. Popular brands are Tube Rose and Navy.

The second, and more popular in North America, variety of snuff is moist snuff, or dipping tobacco. This practice is known as "dipping." In the Southern states, taking a "dip" of moist snuff is called "putting a rub in," the moist snuff in the mouth is known as a "rub." This is occasionally referred to as "snoose" in New England and the Midwest and is derived from the Scandinavian word for snuff, "snus". Like the word, the origins of moist snuff are Scandinavian, and the oldest American brands indicate that by their names. Snuff is also called a "ding" in New England (i.e. "Packing a ding"). American Moist snuff is made from dark fire-cured tobacco that is ground, sweetened, and aged by the factory. Prominent North American brands are Copenhagen, Skoal, Timber Wolf, Chisholm, Grizzly, and Kodiak. American moist snuff tends to be dipped.

Some modern smokeless tobacco brands, such as Kodiak, have an aggressive nicotine delivery. This is accomplished with a higher dose of nicotine than cigarettes, a high pH level (which helps nicotine enter the blood stream faster), and a high portion of unprotonated (free base) nicotine.

It has been suggested by The Economist magazine that the ban on smoking tobacco indoors in some areas, such as Britain and New York City, may lead to a resurgence in the popularity of snuff as an alternative to tobacco smoking. Although the large-scale closure of British mines in the 1980s deprived the snuff industry of its major market since snuff became unfashionable (miners took snuff underground instead of smoking to avoid lethal explosions and fires), sales at Britain's largest snuff retailer have reportedly been rising at about 5% per year. [3]

Chewing tobacco

Chewing is one of the oldest ways of consuming tobacco leaves. Native Americans in both North and South America chewed the leaves of the plant, frequently mixed with lime. Modern chewing tobacco is produced in three forms: twist, plug, and scrap. A few manufacturers in the United Kingdom produce particularly strong twist tobacco meant for use in smoking pipes rather than chewing. These twists are not mixed with lime although they may be flavored with whisky, rum, cherry or other flavors common to pipe tobacco.

Twist is the oldest form. One to three high-quality leaves are braided and twisted into a rope while green, and then are cured in the same manner as other tobacco. Originally devised by sailors due to fire hazards of smoking at sea; and until recently this was done by farmers for their personal consumption in addition to other tobacco intended for sale. Modern twist is occasionally lightly sweetened. It is still sold commercially, but rarely seen outside of Appalachia. Popular brands are Mammoth Cave, Moore's Red Leaf, and Cumberland Gap. Users cut a piece off the twist and chew it, expectorating.

Plug chewing tobacco is made by pressing together cured tobacco leaves in a sweet (often molasses-based) syrup. Originally this was done by hand, but since the second half of the 19th century leaves were pressed between large tin sheets. The resulting sheet of tobacco is cut into plugs. Like twist, consumers sometimes cut, but more often bite off a piece of the plug to chew. Major brands are Days O Work and Cannonball.

Scrap, or looseleaf chewing tobacco, was originally the excess of plug manufacturing. It is sweetened like plug tobacco, but sold loose in bags rather than a plug. Looseleaf is by far the most popular form of chewing tobacco. Popular brands are Red Man, Beechnut, Mail Pouch and Southern Pride. Looseleaf chewing tobacco can also be dipped.

During the peak of popularity of chewing tobacco in the Western United States in the late 19th century, spittoons were a common device for users to spit into.

Snus

Swedish snus is different in that it is made from steam-cured tobacco, rather than fire-cured, and its health effects are markedly different, with epidemiological studies showing

dramatically lower rates of cancer and other tobacco-related health problems than cigarettes, American "Chewing Tobacco", Indian Gutka or African varieties. Prominent Swedish brands are Swedish Match, Ettan, and Tre Ankare. In the Scandinavian countries, moist snuff comes either in loose powder form, to be pressed into a small ball or ovoid either by hand or with the use of a special tool. It is sometimes packaged in small bags, suitable for placing inside the upper lip, called "portion snuff". In the United States, the Skoal brand of moist snuff distributes a similar product, packed with standard american moist snuff, often flavored with fruits or liquors; these small bags are called "Skoal Bandits." These small bags keep the loose tobacco from becoming lodged between the user's teeth; they also generate less spittle when in contact with mucous membranes inside the mouth which extends the usage time of the tobacco product.

Since it is not smoked, snuff in general generates less of the nitrosamines and other carcinogens in the tar that forms from the partially anaerobic reactions in the smoldering smoked tobacco. The steam curing of snus rather than fire-curing or flue-curing of other smokeless tobaccos has been demonstrated to generate even fewer of such compounds than other varieties of snuff; 2.8 parts per mil for Ettan brand compared to as high as 127.9 parts per mil in American brands, according to a study by the State of Massachusetts Health Department. It is hypothesized that the widespread use of snus by Swedish men (estimated at 30% of Swedish men, possibly because it is much cheaper than cigarettes), displacing tobacco smoking and other varieties of snuff, is responsible for the incidence of tobacco-related mortality in men being significantly lower in Sweden than any other European country. In contrast, since women are much less likely to use snus, their rate of tobacco-related deaths in Sweden is similar to that in other European countries. Snus is clearly less harmful than other tobacco products; according to Kenneth Warner, director of the University of Michigan Tobacco Research Network,

"The Swedish government has studied this stuff to death, and to date, there is no compelling evidence that it has any adverse health consequences. ... Whatever they eventually find out, it is dramatically less dangerous than smoking."

Public health researchers maintain that, nevertheless, even the low nitrosamine levels in snus cannot be completely risk free, but snus proponents maintain that inasmuch as snus is used as a substitute for smoking or a means to quit smoking, the net overall effect is positive, similar to the effect of nicotine patches, for instance. Snus is banned in the European Union countries outside of Sweden (regular snus, not portion, is allowed in Denmark and snus is also becoming a regular among Norwegians, as cigarettes are seen by Norwegian popular culture as untrendy and much more unhealthy than snus). Although this is officially for health reasons, it is widely regarded, in fact, as being for economic reasons, since other smokeless tobacco products (mainly from India) associated with much greater risk to health are sold too.

Although it lacks the carcinogenicity of high levels of nitrosamines, however, any harmful effects of nicotine will still be seen with snus usage. Current research concentrates on nicotine's effect on the circulatory system and on the pancreas.

On June 11, 2006, Reynolds Tobacco announced that it would be test marketing Camel brand snus in Portland, Oregon and Austin, Texas by the end of the month. The product

would be manufactured in Sweden, in conjunction with British American Tobacco, manufacturers of BAT snus. [6] gawith apricot snuff

Gutka

Gutka is a tobacco product manufactured and used mainly in India. It contains sweeteners, food coloring and paan flavorings . It is used by constantly chewing without swallowing the juices and then spitting the juices out once the mouth is full of the liquid. This results in the walls of most public buildings to be covered in red stains called pichkari, especially in areas where males from lower income levels congregate.

Creamy snuff

Creamy snuff is a tobacco paste, consisting of tobacco, clove oil, glycerin, spearmint, menthol, and camphor, and sold in a toothpaste tube. It is marketed mainly to women in India, and is known by the brand names Ipco (made by Asha Industries), Denobac, Tona, Ganesh. It is locally known as "mishri" in some parts of Maharashtra. According to the U.S NIH-sponsored 2002 Smokeless Tobacco Fact Sheet, it is marketed as a dentifrice. The same factsheet also mentions that it is "often used to clean teeth. The manufacturer recommends letting the paste linger in the mouth before rinsing."

Tobacco water

Tobacco water is a traditional organic insecticide used in domestic gardening. Tobacco dust can be used similarly.

It is produced by boiling strong tobacco in water, or by steeping the tobacco in water for a longer period. When cooled the mixture can be applied as a spray, or 'painted' on to the leaves of garden plants, where it will prove deadly to insects.

Basque angulero fishermen kill immature eels (elvers) in an infusion of tobacco leaves before parboiling them in salty water for transportation to market as angulas, a seasonal delicacy.[7]

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See also

- Nicotine

Notes

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3. ^ The Economist: Thou shalt not inhale, Issue 8465, February 18th, pg 28

Curare

Curare is a common name for various dart poisons originating from South America. The three main types, or famillies of curare are: the tubocurare (also known as tube or bamboo curare, because of its packing into hollow bamboo tubes; main toxin is D-tubocurarine), the calebas curare (also called "gourd curare" by older british classifications, beeing packed into hollow gourds; main toxins are alloferine and toxiferine) and the pot curare (packed in terracota pots; main toxins are protocurarine, protocurine, and protocuridine). Of these

three families, some formulas belonging to the calebas curare are the most toxic, relative to their LD***50*** values.

The most known and historically (because of its medical applications) important toxin is however the D-tubocurarine. It was introduced into anesthesiology in early 1940s as a muscle relaxant for surgery. It is important to know, that curares are active (i.e. toxic or muscle relaxing, dependant on the intention of their use) only if given/applied parenterally, that is, by an injection, or direct wound contamination by poisoned dart/arrow tip. Upon ingestion (per os), curares are inactive. This is crucial, because the native tribes use curares mainly for hunting purposes, thus the poisoned prey must be innoxious upon eating. In medicine, curare has been superseded by a number of curare-like agents (examples are succinylcholine, also called suxamethonium, and pancuronium, an alkaloid-like substance with steroidal skeleton in its molecule), that have a similar pharmacodynamic profile but with fewer side effects.

Curare is an example of a non-depolarizing muscle relaxant which blocks the nicotinic receptors, one of the two types of cholinergic (acetylcholine) receptors on the post synaptic membrane of the neuromuscular junction.

Curare has also been used historically as a paralyzing poison by South American indigenous people. The prey is killed by asphyxiation as the respiratory muscles are unable to contract resulting in apnea.

Curare and anaesthesia

Muscle relaxants are used in modern anaesthesia for many reasons, such as providing optimal operating conditions and facilitating intubation of the trachea. Before muscle relaxants, anaesthesiologists needed to use larger doses of the anaesthetic agent, such as ether or cyclopropane to achieve these aims. Such deep anaesthesia risked killing patients that were elderly or had heart conditions.

The source of curare in the Amazon was first researched by Richard Evans Schultes in 1941. Since the 1930s, it was being used in hospitals as a muscle relaxant. He discovered that different types of curare called for as many as 15 ingredients, and in time helped to identify more than 70 species that produced the drug [1].

On January 23, 1942, Dr. Harold Griffith and Dr. Enid Johnson gave a synthetic preparation of curare (Intracostin) to a patient undergoing an appendectomy (to supplement conventional anaesthesia). Modern anaesthetists have at their disposal a variety of muscle relaxants for use as a standard component of anaesthesia.

The ability to produce muscle relaxation independently from anaesthesia has permitted anaesthesiologists to adjust the two effects as needed to ensure that their patients are safely unconscious and sufficiently relaxed to permit surgery. However, it has also made possible anaesthesia awareness, a condition in which, through error or accident, a patient remains fully conscious and sensitive to pain during surgery, but is unable to move and thus unable to alert attending staff to their state of awareness.

Plants from which primary components of curare can be extracted

- Strychnos toxifera
Chondrodendron tomentosum

Anticoagulant

An *anticoagulant* is a substance that prevents coagulation; that is, it stops blood from clotting. A group of pharmaceuticals called anticoagulants can be used in vivo as a medication for thrombotic disorders. Some chemical compounds are used in medical equipment, such as test tubes, blood transfusion bags, and renal dialysis equipment..

As medications

Anticoagulants are given to people to stop thrombosis (blood clotting inappropriately in the blood vessels). This is useful in primary and secondary prevention of deep vein thrombosis, pulmonary embolism, myocardial infarctions and strokes in those who are predisposed.

Vitamin K antagonists

The oral anticoagulants are a class of pharmaceuticals that act by antagonizing the effects of vitamin K. It is important to note that they take at least 48 to 72 hours for the anticoagulant effect to develop fully. In cases when an immediate effect is required, heparin must be given concomitantly. Generally, these anticoagulants are used to treat patients with deep-vein thrombosis (DVT), pulmonary embolism, atrial fibrillation, and mechanical prosthetic heart valves.

These oral anticoagulants are used widely as poisons for mammalian pests, especially rodents. (For details, see rodenticide and warfarin.)

The most important oral anticoagulants are:

- Warfarin (Coumadin). This is the main agent used in the U.S. and UK
- Acenocoumarol and phenprocoumon This is used more commonly outside the U.S. and the UK
- Phenindione

Heparin and derivative substances

Heparin is a biological substance, usually made from pig intestines. It works by activating antithrombin III, which blocks thrombin from clotting blood. Heparin can be used in vivo (by injection), and also in vitro to prevent blood or plasma clotting in medical devices. Vacutainer brand test tubes containing heparin are usually colored green.

Low molecular weight heparin is a more highly processed product that is useful as it does not require monitoring of the APTT coagulation parameter (it has more predictable plasma levels) and has less side effects.

Fondaparinux is a synthetic sugar composed of the five sugars (pentasaccharide) in heparin that bind to antithrombin. It is a smaller molecule than low molecular weight heparin.

Direct thrombin inhibitors

Another type of anticoagulant is the direct thrombin inhibitors. Current members of this class include argatroban, lepirudin, and bivalirudin. An oral direct thrombin inhibitor, ximelagatran (Exanta®) may replace warfarin for some indications. It is awaiting Food and Drug Administration (FDA) approval.

Anticoagulants outside the body

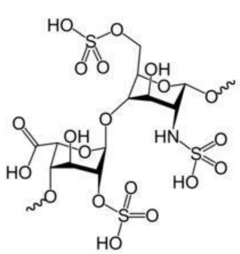
Laboratory instruments, test tubes, blood transfusion bags, and medical and surgical equipment will get clogged up and become nonoperational if blood is allowed to clot. Chemicals can be added to stop blood clotting. Apart from heparin, most of these chemicals work by binding calcium ions, preventing the coagulation proteins from using them.

- EDTA is denoted by mauve or purple caps on Vacutainer brand test tubes. This chemical strongly and irreversibly binds calcium. It is in a powdered form.

  Citrate is usually in blue Vacutainer tube. It is in liquid form in the tube and is used for coagulation tests, as well as in blood transfusion bags. It gets rid of the calcium, but not as strongly as EDTA. Correct proportion of this anticoagulant to blood is crucial because of the dilution. It can be in the form of sodium citrate or ACD.

  Oxalate has a similar mechanism to citrate. It is the anticoagulant used in fluoride (grey top) tubes.

Heparin



Identifiers

CAS number 9005-49-6

ATC code B01**AB01** C05**BA03** S01**XA14**

PubChem 772

DrugBank APRD00056

Chemical data

Formula mixed polymeric (for skeletal structure shown above C***12***H***19***NO***20***S***3***)

Mol. weight 12000-15000 g/mol

Pharmacokinetic data

Bioavailability **nil**

Metabolism hepatic

Therapeutic considerations

Routes i.v., s.c.

Heparin is a highly sulfated glycosaminoglycan widely used as an injectable anticoagulant. It is also used to form an inner anticoagulant surface on various experimental and medical devices such as test tubes and renal dialysis machines. Pharmaceutical grade heparin is commonly derived from mucosal tissues of slaughtered meat animals such as porcine intestine or bovine lung.[1]

Heparin structure

Native heparin is a polymer with a molecular weight ranging from 3 kDa to 40 kDa although the average molecular weight of most commercial heparin preparations is in the range of 12 kDa to 15 kDa. Heparin is a member of the glycosaminoglycan family of carbohydrates (which includes the closely related molecule heparan sulfate) and consists of a variably sulfated repeating disaccharide unit. The main disaccharide units that occur in heparin are shown below. The most common disaccharide unit is composed of a 2-O-sulfated iduronic acid and 6-O-sulfated, N-sulfated glucosamine, IdoA(2S)-GlcNS(6S). For example this makes up 85% of heparins from beef lung and about 75% of those from porcine intestinal mucosa. Not shown below are the rare disaccaharides containing a 3-O-sulfated glucosamine (GlcNS(3S,6S) or a free amine group (GlcNH3+). Under physiological conditions the ester and amide sulfate groups are deprotonated and attract positively charged counterions to form a heparin salt. It is in this form that heparin is usually administered as an anticoagulant.

Abbreviations

- *GlcA* = ²-L-glucuronic acid
- *IdoA* = ±-L-iduronic acid
- *IdoA(2S)* = 2-O-sulfo-±-L-iduronic acid
- *GlcNAc* = 2-deoxy-2-acetamido-±-D-glucopyranosyl
- *GlcNS* = 2-deoxy-2-sulfamido-±-D-glucopyranosyl
- *GlcNS(6S)* = 2-deoxy-2-sulfamido-±-D-glucopyranosyl-6-O-sulfate

Three-dimensional structure

The three dimensional structure of heparin is complicated by the fact that iduronic acid may be present in either of two low energy conformations when internally positioned within an oligosaccharide. The conformational equilibrium being influenced by sulfation state of adjacent glucosamine sugars.[2] Nevertheless the solution structure of a heparin dodecasacchride composed solely of six GlcNS(6S)-IdoA(2S) repeat units has been determined using a combination of NMR spectroscopy and molecular modelling techniques.[3] Two models were constructed one in which all IdoA(2S) were in the 2S0 conformation (A and B below) and one in which they are in the 1C4 conformation (C and D below). However there is no evidence to suggest changes between these conformations occurs in a concerted fashion. These models correspond to the protein data bank code 1HPN

In these models heparin adopts a helical conformation, the rotation of which places clusters of sulfate groups at regular intervals of about 17 angstroms (1.7 nm) on either side of the helical axis.

Medical use

Heparin acts as an anticoagulant, preventing the formation of clots and extension of existing clots within the blood. While heparin does not break down clots that have already formed, it allows the body's natural clot lysis mechanisms to work normally to break down clots that have already formed. Heparin is used for anticoagulation for the following conditions:

- Acute coronary syndrome, e.g., myocardial infarction

Atrial fibrillation

Deep-vein thrombosis and pulmonary embolism.

History

Heparin is one of the oldest drugs currently still in widespread clinical use. As it was discovered in 1916, its introduction predates the establishment of the United States Food and Drug Administration.[4] It was originally isolated from liver cells, hence its name (hepar or "·À±Á" is Greek for "liver"). Scientists were looking for an anticoagulant that could work safely in humans, and Jay McLean, a second-year medical student from Johns Hopkins University working under the guidance of William Henry Howell, found a compound extracted from liver that acted as an anticoagulant.

Administration

Heparin is given parenterally; it is digested when taken by mouth. It can be injected intravenously or subcutaneously (under the skin). Intramuscular injections (into muscle) are avoided because of the potential for forming hematomas. Because of its short biologic half-life of approximately one hour, heparin must be given frequently or as a continuous infusion.

If long-term anticoagulation is required, heparin is often only used to commence anticoagulation therapy until the oral anticoagulant warfarin takes effect.

Adverse reactions

A serious side-effect of heparin is heparin-induced thrombocytopenia (HIT syndrome). HITS is caused by an immunological reaction that makes platelets aggregate within the blood vessels, thereby using up coagulation factors. Formation of platelet clots can lead to thrombosis, while the loss of coagulation factors and platelets may result in bleeding. HITS can (rarely) occur shortly after heparin is given, but also when a person has been on heparin for a long while. Immunologic tests are available for the diagnosis of HITS. There is also a benign form of thrombocytopenia associated with early heparin use which resolves without stopping heparin.

Other side effects include alopecia and osteoporosis.

As with many drugs, overdoses of Heparin can be fatal. In September 2006, Heparin received worldwide publicity when 3 prematurely-born infants died after they were mistakenly given adult-sized doses of Heparin at an Indianapolis hospital.[5]

Treatment of overdose

In case of overdose, protamine sulfate can be given to counteract the action of heparin.

Mechanism of action

Heparin is a naturally occurring anticoagulant produced by basophils and mast cells. [6] Heparin binds to the enzyme inhibitor antithrombin III (AT-III) causing a conformational change which results in its active site being exposed. The activated AT-III then inactivates thrombin and other proteases involved in blood clotting, most notably factor Xa. The rate of inactivation of these proteases by AT-III increases 1000-fold due to the binding of heparin.[7]

AT-III binds to a specific pentasaccharide sulfation sequence contained within the heparin polymer

GlcNAc/NS(6S)-GlcA-GlcNS(3S,6S)-IdoA(2S)-GlcNS(6S)

The conformational change in AT-III on heparin binding mediates its inhibition of factor Xa. For thrombin inhibition however, thrombin must also bind to the heparin polymer at a site proximal to the pentasacchride. The formation of a ternary complex between AT-III, thrombin and heparin results in the inactivation of thrombin. For this reason heparin's activity against thrombin is size dependent, the ternary complex requiring at least 18 saccharide units for efficient formation.[8] In contrast anti factor Xa activity only requires the pentasacchride binding site.

This size difference has led to the development of low molecular weight heparins and more recently to fondaparinux (a synthetic pentasacchride identical in structure to the AT-III binding pentasacchride) as pharmaceutical anticoagulants. These products target anti

factor Xa activity rather than anti thrombin (IIa) activity with the aim of facilitating a more subtle regulation of coagulation and an improved therapeutic index.

With these fractioned heparin alternatives, there is a reduced risk of osteoporosis and heparin-induced thrombocytopenia (HIT). Monitoring of the APTT is also not required and indeed does not reflect the anticoagulant effect, as APTT is insensitive to alterations in factor Xa.

Danaparoid, a mixture of heparan sulfate, dermatan sulfate and chondroitin sulfate can be used as an anticoagulant in patients who have developed HIT. Because danaparoid does not contain heparin or heparin fragments cross-reactivity of danaparoid with heparin-induced antibodies is reported as less than 10% (see here)

The effects of heparin are measured in the lab by the partial thromboplastin time (aPTT), (the time it takes the blood plasma to clot).

Heparin's exact physiological role is still unclear, because blood anti-coagulation is mostly achieved by endothelial cell-derived heparan sulfate proteoglycans.[9]

Heparin gel

Heparin gel (topical) may sometimes be used to treat sports injuries. It is known that the diprotonated form of histamine binds site specifically to heparin.[10] The release of histamine from mast cells at a site of tissue injury contributes to an inflammatory response. The rationale behind the use of such topical gels may be to block the activity of released histamine and so help to reduce inflammation.

Other uses/information

- Test tubes, Vacutainers, and capillary tubes that use the lithium salt of heparin (lithium heparin) as an anticoagulant are usually marked with green stickers and green tops. Heparin has the advantage over EDTA as an anticoagulant, as it does not affect levels of ions (such as calcium). Heparin can interfere with some immunoassays, however. As lithium heparin is usually used, a person's lithium levels cannot be obtained from these tubes; for this purpose, royal-blue topped Vacutainers containing sodium heparin are used.
- Heparin-coated blood oxygenators are available for use in heart-lung machines. Among other things, these specialized oxygenators are though to improve overall biocompatibility and host homeostasis by providing characteristics similar to native endothelium.
- Common diagnostic procedures require PCR amplification of a patient's DNA, which is easily extracted from white blood cells treated with heparin. This poses a potential problem, since heparin may be extracted along with the DNA, and it has been found to interfere with the PCR reaction at levels as low as 0.002 U in a 50 ¼L reaction mixture.[11]

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Warfarin

Systematic (IUPAC) name

(RS)-4-hydroxy-3-(3-oxo-1-phenylbutyl)-2H-chromen-2-one

Identifiers

CAS number 81-81-2

ATC code B01**AA03**

PubChem 6691

DrugBank APRD00341

Chemical data

Formula $C_{19}H_{16}O_4$

Mol. weight 308.33 g/mol

Pharmacokinetic data

Bioavailability **100%**

Protein binding 99.5%

Metabolism Hepatic: CYP2C9, 2C19, 2C8, 2C18, 1A2 and 3A4

Half life 2.5 days

Excretion Renal (92%)

Therapeutic considerations

Pregnancy cat. $D_{(AU)}$ $X_{(US)}$

Legal status $S4_{(AU)}$ $POM_{(UK)}$ $_{\text{-only(US)}}$

Routes Oral

Warfarin (also known under the brand names of *Coumadin*®, *Jantoven*®, *Marevan*®, and *Waran*®) is an anticoagulant medication that is administered orally or, very rarely, by injection. It is used for the prophylaxis of thrombosis and embolism in many disorders. Its activity has to be monitored by frequent blood testing for the international normalized ratio (INR). It is named for the Wisconsin Alumni Research Foundation.

Warfarin is a synthetic derivative of coumarin, a chemical found naturally in many plants, notably woodruff (Galium odoratum, Rubiaceae), and at lower levels in licorice, lavender and various other species. Warfarin was originally developed as a rat poison, but it is no longer used for that purpose as modern poisons are much more potent and toxic (e.g. brodifacoum). However, warfarin and contemporary rodenticides belong to the same class of drugs (coumarins) and both decrease blood coagulation by interfering with vitamin K metabolism.

Mechanism of action

Warfarin inhibits the synthesis of biologically active forms of the vitamin K-dependent clotting factors: II, VII, IX and X, as well as the regulatory factors protein C, protein S and protein Z. Other proteins not involved in blood clotting, such as osteocalcin, or matrix Gla protein, may also be affected.

The precursors of these factors require carboxylation of their glutamic acid residues to allow the coagulation factors to bind to phospholipid surfaces inside blood vessels, on the vascular endothelium. This enzyme that carries out the carboxylation of glutamic acid is the gamma-glutamyl carboxylase. The carboxylation reaction will only proceed if the carboxylase enzyme is able to convert a reduced form of Vitamin K (Vitamin K hydroquinone) to vitamin K epoxide at the same time. The Vitamin K epoxide is in turn recycled back to Vitamin K and Vitamin K hydroquinone by another enzyme, the vitamin K epoxide reductase (VKOR). Warfarin inhibits epoxide reductase[1] (specifically the VKORC1 subunit[2][3]), thereby diminishing available vitamin K and Vitamin K hydroqunone in the tissues, which inhibits the carboxylation activity of the glutamyl carboxylase. When this occurs, the coagulation factors are no longer carboxylated at certain glutamic acid residues, and are incapable of binding to the endothelial surface of blood vessels, and are thus biologically inactive. As the body stores of previously-produced active factors degrade (over several days) and are replaced by inactive factors, the anticoagulation effect becomes apparent. The coagulation factors are produced, but have decreased functionality due to undercarboxylation; they are collectively referred to as PIVKAs (proteins induced [by] vitamin K absence/antagonism). Hence, the effect of warfarin is to diminish blood clotting in the patient.

Uses

Medical use

Warfarin is prescribed to people with an increased tendency for thrombosis or as prophylaxis in those individuals who have already formed a blood clot (thrombus) which required treatment. This can help prevent formation of future blood clots and help reduce the risk of embolism (migration of a thrombus to a spot where it blocks blood supply to a vital organ). Common clinical indications for warfarin use are atrial fibrillation, artificial heart valves, deep venous thrombosis and pulmonary embolism.[4]

Dosing of warfarin is complicated by the fact that it is known to interact with many commonly used medications and other chemicals that may be present in appreciable quantities in food. These interactions may enhance or reduce warfarin's anticoagulation effect. Many commonly used antibiotics, such as metronidazole or the macrolides, will greatly increase the effect of warfarin by reducing the metabolism of warfarin in the body. Other broad-spectrum antibiotics can reduce the amount of the normal bacterial flora in the bowel, which make significant quantities of Vitamin K, thus potentiating the effect of warfarin. In addition, food that contains large quantities of Vitamin K will reduce the warfarin effect; and medical conditions such as hypo- or hyperthyroidism will alter the rate of breakdown of the clotting factors.

Therefore, in order to optimise the therapeutic effect without risking dangerous side effects, such as bleeding, close monitoring of the degree of anticoagulation is required by blood testing (INR). Initially, checking may be as often as twice a week; the intervals can be lengthened if the patient manages stable therapeutic INR levels on an unchanged warfarin dose.

When initiating warfarin therapy ("warfarinisation"), the doctor will decide how strong the anticoagulant therapy needs to be. The target INR level will vary from case to case dependent upon the clinical indicators, but tends to be 2-3 in most conditions.

The oral anticoagulant ximelagatran (Exanta®) was expected to replace warfarin to a large degree when introduced; however, reports of hepatotoxicity (liver damage) prompted its manufacturer to withdraw it from further development. Other drugs offering the efficacy of warfarin without a need for monitoring, such as dabigatran and rivaroxaban, are under development.

Pesticide use

Coumarins, a class of drugs of which warfarin is a member, are used as a rodenticide for controlling rats and mice in residential, industrial, and agricultural areas. The active ingredient in rat poison is brodifacoum, which is sometimes referred to as a super-warfarin, because it is longer acting than the drug warfarin. It is both odorless and tasteless. It is effective when mixed with food bait, because the rodents will return to the bait and continue to feed over a period of days, until a lethal dose is accumulated (considered to be 1 mg/kg b.w./day over four to five days for warfarin; for brodifacoum, no reliable cumulative toxicity datas are available as of time, but it could be concluded, given the similarity with other 4-hydroxycoumarin derivatives, that these would be in order of tens of μg/kg b.w./day for periods of 2-10 days). It may also be mixed with talc and used as a tracking powder, which accumulates on the animal's skin and fur, and is subsequently consumed during grooming. The use as rat poison is now declining because many rat populations have developed resistance to warfarin.

The LD50 is 50–500 mg/kg. The IDLH value is 100mg/m^3 (warfarin; various species). LD***50***(mouse, oral) = 0.40 mg/kg; (rat, oral) = 0.27 mg/kg (brodifacoum). The IDLH value for brodifacoum is not defined, but given the toxicity of brodifacoum, it would be substantialy lower, perhaps less than 1/100 of the warfarin value, i.e. <1 mg/m^3.

Side-effects

The only common side-effect of warfarin is hemorrhage (bleeding). The risk of severe bleeding is small but definite (1-2% annually) and any benefit needs to outweigh this risk when warfarin is considered as a therapeutic measure. Risk of bleeding is augmented if the INR is out of range (due to accidental or deliberate overdose or due to interactions), and may cause hemoptysis (coughing up blood), excessive bruising, bleeding from nose or gums, or blood in urine or stool.

A feared (but rare) complication of warfarin is warfarin necrosis, which occurs more frequently shortly after commencing treatment in patients with a deficiency of protein C. Protein C is an innate anticoagulant that, like the procoagulant factors that warfarin inhibits, requires vitamin K-dependent carboxylation for its activity. Since warfarin initially decreases protein C levels faster than the coagulation factors, it can paradoxically increase the blood's tendency to coagulate when treatment is first begun (many patients when starting on warfarin are given heparin in parallel to combat this), leading to massive

thrombosis with skin necrosis and gangrene of limbs. Its natural counterpart, purpura fulminans, occurs in children who are homozygous for protein C mutations.

Pharmacology

Pharmacokinetics and antagonism

Warfarin consists of a racemic mixture of two active optical isomers - R and S forms - each of which is cleared by different pathways. S-warfarin has five times the potency of the R-isomer with respect to Vitamin K antagonism.[4]

Warfarin is slower acting than the common anticoagulant heparin, though it has a number of advantages. Heparin must be given by injection, while warfarin is available orally. Warfarin has a long half-life and need only be given once a day. Heparin can also cause a prothrombotic condition, heparin-induced thrombocytopenia (an antibody-mediated decrease in platelet levels), which paradoxically increases the risk for thrombosis. Warfarin's long half life, on the other hand, means it often takes several days to reach therapeutic effect. Furthermore, if given initially without additional anticoagulant cover, it can paradoxically increase thrombosis risk. For these main reasons, hospitalised patients are usually given heparin initially, and are then moved on to warfarin.

Warfarin can be reversed with vitamin K, or for rapid reversal (e.g. in case of severe bleeding), with fresh frozen plasma but this treatment is being replaced by use of prothrombin complex concentrate.

Pharmacogenomics

Warfarin activity is determined partially by genetic factors. Polymorphisms in the VKORC1 gene explain 25% of the dose variation between patients: particular mutations make VKORC1 less susceptible to suppression by warfarin.[3][5] CYP2C9 polymorphisms explain another 10%.[5] VKORC1 polymorphisms also explain why African Americans are relatively resistant to warfarin, while Asian Americans are more sensitive.[5]*Small Text*

Loading regimens

Because of warfarin's poorly predictable pharmacokinetics, several researchers have proposed algorithms for commencing warfarin treatment. For urgent anticoagulation, the Fennerty regimen[6] is used commonly, while for "routine" (low-risk) anticoagulation, the Tait regimen[7] is more popular.

Interactions and contraindications

There are many drug-drug interactions with warfarin, and its metabolism varies greatly between patients. Some foodstuffs have also been reported to interact with warfarin[8] This makes finding the correct dosage difficult, and accentuates the need of monitoring; when initiating a medication that is known to interact with warfarin (e.g. amiodarone), INR checks are increased or dosages adjusted until a new ideal dosage is found.

Warfarin cannot be given to pregnant women, especially in the first trimester, as it is a teratogen (it causes deformations of the face and bones). During the third trimester, antepartum hemorrhage can occur. Instead of warfarin, low molecular weight heparin is generally used.

Excessive use of alcohol is also known to affect the metabolism of warfarin, although moderate drinking usually has little or no effect on the INR value. Patients suffering from liver damage or alcoholism are usually treated with heparin injections instead.

Warfarin also interacts with the following herbs: [9]

- Ginkgo (a.k.a. Ginkgo Biloba), which is commonly used to increase brain blood flow, prevent dementia, and improve memory. However, ginkgo may increase blood pressure, and may increase bleeding, especially in people already taking certain anti-clotting medications such as warfarin.
- St. John's Wort is commonly used to help with mild to moderate depression. However, it may prolong the effects of certain anesthetic drugs and reduce the effects oral contraceptives and anti-organ transplant rejection medications, and interfere with warfarin.
- Ginseng is commonly used to help with fatigue and weakness. However, ginseng may increase blood pressure and heart rate and may increase bleeding, especially in people already taking certain anti-clotting medications such as warfarin.
- Garlic (as a supplement, not in the diet) is commonly used to help lower high cholesterol levels, high triglycerides, and high blood pressure. However, may increase bleeding especially in people already taking certain anti-clotting medications such as warfarin.
- Ginger is commonly used to help nausea and poor digestion. However, it may increase bleeding, especially in patients already taking certain anti-clotting medications such as warfarin.

History

The early 1920s saw the outbreak of a previously unrecognized disease of cattle in the northern United States and Canada. Cattle would die of uncontrollable bleeding from very minor injuries, or sometimes drop dead of internal hemorrhage with no external signs of injury. In 1921, Frank Schofield, a Canadian veterinarian, determined that the cattle were ingesting moldy silage made from sweet clover that functioned as a potent anticoagulant.[10] In 1929, North Dakota veterinarian Dr L.M. Roderick demonstrated that the condition was due to a lack of functioning prothrombin.[11]

The identity of the anticoagulant substance in moldy sweet clover remained a mystery until 1940 when Karl Paul Link and his student Harold Campbell, chemists working at the University of Wisconsin, determined that it was the coumarin derivative 4-hydroxycoumarin.[12] Over the next few years, numerous similar chemicals were found to have the same anticoagulant properties. The first of these to be widely commericialized was dicoumarol, patented in 1941. Link continued working on developing more potent coumarin-based anticoagulants for use as rodent poisons, resulting in warfarin in 1948. (The

name warfarin stems from the acronym WARF, for Wisconsin Alumni Research Foundation + the ending -arin indicating its link with coumarin. Warfarin was first registered for use as a rodenticide in the US in 1952; although it was developed by Link, the WARF financially supported the research and was granted the patent.

The exact mechanism of action remained unknown until it was demonstrated, in 1978, that warfarin inhibited epoxide reductase and hence interfered with vitamin K metabolism.[1]

After an incident in 1951, where a naval enlisted man unsuccessfully attempted suicide with warfarin and recovered fully, studies began in the use of warfarin as a therapeutic anticoagulant. It was found to be generally superior to dicoumarol, and in 1954 was approved for medical use in humans. A famous early patient prescribed warfarin was Dwight Eisenhower, president of the USA, subsequent to his heart attack in 1955.

A 2003 theory posits that warfarin was used by a conspiracy of Lavrenty Beria, Nikita Khrushchev and others to poison Soviet leader Joseph Stalin. Warfarin is tasteless and colorless, and produces symptoms similar to those that Stalin exhibited.[13]

Other coumarins

In some countries, other coumarins are used instead of warfarin, such as acenocoumarol and phenprocoumon. These have a shorter (acenocoumarol) or longer (phenprocoumon) half-life, and are not completely interchangeable with warfarin.

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Anticonvulsants

The *anticonvulsants*, sometimes also called *antiepileptics*, belong to a diverse group of pharmaceuticals used in prevention of the occurrence of epileptic seizures. The goal of an anticonvulsant is to suppress the rapid and excessive firing of neurons that start a seizure. Failing this, a good anticonvulsant would prevent the spread of the seizure within the brain and offer protection against possible excitotoxic effects that may result in brain damage. An excellent anticonvulsant would have few serious side effects. However, no such drug exists.

Many anticonvulsants block Sodium (Na+) channels, Calcium (Ca2+) channels, AMPA receptors or NMDA receptors. Some anticonvulsants inhibit the metabolism of GABA or increase its release.

In the following list, the dates in parentheses are the earliest approved use of the drug.

Aldehydes

- Paraldehyde (1882). One of the earliest anticonvulsants. Still used to treat status epilepticus, particularly where there are no resuscitation facilities.

Aromatic allylic alcohols

- Stiripentol (2001 - limited availability). Indicated for the treatment of severe myoclonic epilepsy in infancy (SMEI).

Barbiturates

Main article: Barbiturates

Barbiturates are drugs that act as central nervous system (CNS) depressants, and by virtue of this they produce a wide spectrum of effects, from mild sedation to anesthesia. The following are classified as anticonvulsants:

- Phenobarbital (1912). See also the related drug primidone.
- Methylphenobarbital (1935). Known as mephobarbital in the US. No longer marketed in the UK
- Metharbital (1952). No longer marketed in the UK or US.
- Barbexaclone (1982). Only available in some European countries.

Phenobarbital was the main anticonvulsant from 1912 till the development of phenytoin in 1938. Today, phenobarbital is rarely used to treat epilepsy in new patients since there are other effective drugs that are less sedating. Phenobarbital sodium injection can be used to stop acute convulsions or status epilepticus, but a benzodiazepine such as lorazepam, diazepam or midazolam is usually tried first. Other barbiturates only have an anticonvulsant effect at anaesthetic doses.

Benzodiazepines

Main article: Benzodiazepines

The benzodiazepines are a class of drugs with hypnotic, anxiolytic, anticonvulsive, amnestic and muscle relaxant properties. The relative strength of each of these properties in any given benzodiazepine varies greatly and influences the indications for which it is prescribed. Long-term use can be problematic due to the development of tolerance and dependency. Of the many drugs in this class, only a few are used to treat epilepsy:

- Clobazam (1979). Notably used on a short-term basis around menstruation in women with catamenial epilepsy. Clonazepam (1974). Clorazepate (1972).

The following benzodiazepines are used to treat status epilepticus:

- Diazepam (1963). Can be given rectally by trained care-givers.
- Midazolam (N/A). Increasingly being used as an alternative to diazepam. This water-soluble drug is squirted into the side of the mouth but not swallowed. It is rapidly absorbed by the buccal mucosa.
- Lorazepam (1972). Given by injection in hospital.

Bromides

- Potassium bromide (1857). The earliest effective treatment for epilepsy. There would not be a better drug for epilepsy until phenobarbital in 1912. It is still used as an anticonvulsant for dogs and cats.

Carbamates

- Felbamate (1993). This effective anticonvulsant has had its usage severely restricted due to rare but life-threatening side effects.

Carboxamides

Main article: Carboxamides

The following are carboxamides:

- Carbamazepine (1965). A popular anticonvulsant that is available in generic formulations. Oxcarbazepine (1990). A derivative of carbamazepine that has similar efficacy but is better tolerated.

Fatty acids

The following are fatty-acids:

- The valproates — valproic acid, sodium valproate, and divalproex sodium (1978).

Vigabatrin (1989).
Progabide
Tiagabine (1997).

Vigabatrin and progabide are also analogs of GABA.

Fructose derivatives

- Topiramate (1995).

Gaba analogs

- Gabapentin (1993).
Pregabalin (2004).

Hydantoins

The following are hydantoins:
- Ethotoin (1957).
Phenytoin (1938).
Mephenytoin
Fosphenytoin (1996).

Oxazolidinediones

The following are oxazolidinediones:
- Paramethadione
Trimethadione (1946).
Ethadione

Propionates

- Beclamide

Pyrimidinediones

- Primidone (1952).

Pyrrolidines

- Brivaracetam
Levetiracetam (1999).
Seletracetam

Succinimides

The following are succinimides:

- Ethosuximide (1955).

Phensuximide
Mesuximide

Sulfonamides

Main article: Sulfonamides

- Acetazolamide (1953).

Sulthiame
Methazolamide
Zonisamide (1990).

Triazines

- Lamotrigine (1991).

Ureas

- Pheneturide

Phenacemide

Valproylamides (amide derivatives of valproate)

- Valpromide

Valnoctamide

Barbiturates

Barbiturates are drugs that act as central nervous system (CNS) depressants, and by virtue of this they produce a wide spectrum of effects, from mild sedation to anesthesia. Some are also used as anticonvulsants.

Barbiturates are believed to be GABA (gamma-aminobutyric acid) agonists, acting on the GABA-A receptor. GABA is the principal inhibitory neurotransmitter in the mammalian CNS.

Barbiturates are derivatives of barbituric acid.

Medical uses

Today barbiturates are infrequently used as anticonvulsants and for the induction of anesthesia. Benzodiazepines were made as safer barbiturate alternatives as they are virtually impossible to overdose and thus help thwart individuals with suicidal tendencies. Since the introduction of Diazepam in 1963, the first benzodiazepine prescibed for clinical

use, barbiturates have been gradually phased out from use. Some of the barbiturates available are:

- Amobarbital (Sodium Amytal; hypnotics)

Aprobarbital (hypnotic)
Butabarbital (hypnotics)
Butalbital (Fiorinal; sedative)
Hexobarbital (Sombulex; hypnotic/anesthetic)
Methylphenobarbital (Mebaral; antianxiety, anticonvulsant)
Pentobarbital (Nembutal; hypnotic)

- Phenobarbital (Luminal; hypnotic, sedative, anticonvulsant)
- Secobarbital (Seconal; hypnotic)

Sodium thiopental
Talbutal (Lotusate; hypnotic)
Thiobarbital (anesthetic)

Sometimes two or more barbiturates are combined in a single tablet or capsule; perhaps the most well-known of these combinations is Tuinal, which consists of amobarbital and secobarbital in equal proportions.

Recreational use

Barbiturates were very popular in the first half of the twentieth century. In moderate amounts, these drugs produce a state of intoxication that is remarkably similar to alcohol intoxication. Symptoms include slurred speech, loss of motor coordination, and impaired judgment. Depending on the dose, frequency, and duration of use, one can rapidly develop tolerance, physical dependence, and psychological dependence on barbiturates. With the development of tolerance, the margin of safety between the effective dose and the lethal dose becomes very narrow. That is, in order to obtain the same level of intoxication, the tolerant abuser may raise his or her dose to a level that may result in coma or death. Although many individuals have taken barbiturates therapeutically without harm, concern about the addiction potential (withdrawal symptoms can include tonic-clonic or grand mal seizures potentially leading to permanent disability or even death) of barbiturates and the ever-increasing number of fatalities associated with them led to the development of alternative medications, namely benzodiazepines. Today, fewer than 10 percent of all sedative/hypnotic prescriptions in the United States are for barbiturates.

Other non-therapeutical use

Barbiturates in high doses are used for physician-assisted suicide (PAS). In combination with a muscle relaxant, for euthanasia and for capital punishment by lethal injection.

History

- Dec 4, 1863 Barbituric acid is discovered by German researcher Adolf von Baeyer. His discovery came on the day of St. Barbara, the patron saint of chemistry, so he chose the name "barbiturate" as a combination of St. Barbara

and "urea". Another possible explanation is that he named the substance after his girlfriend Barbara.

- 1903 Barbital, the first medicinal barbiturate, is synthesized from barbituric acid by German scientists Emil Hermann Fischer and Joseph von Mering. It was marketed under the trade name Veronal.
- 1912 Phenobarbital is introduced under the trade name Luminal as a sedative-hypnotic.
- 1950s - 1960s Reports increase about side effects and dependence related to barbiturates.
- 1970 Pentobarbital (II), secobarbital (II), amobarbital (II), butabarbital (III), phenobarbital (IV), and barbital (IV) are all scheduled with the passage of the U.S. Drug Abuse Regulation and Control Act of 1970.
- 1971 Convention on Psychotropic Substances is signed in Vienna. Designed to regulate amphetamines, barbiturates, and other synthetics, the treaty today regulates amobarbital (III), butalbital (III), cyclobarbital (III), pentobarbital (III), allobarbital (IV), methylphenobarbital (IV), phenobarbital (IV), secbutabarbital (IV), and vinylbital (IV) as scheduled substances.

Poisoning

Barbiturates are sedatives used for seizure disorders, induction of anesthesia, and management of increased intracranial pressure. Barbiturates enhance the inhibitory neurotransmitter gamma amino butyric acid (GABA) and are general depressants to nerve and muscle tissue. Mild to moderate barbiturate toxicity mimics alcohol intoxication. Severe acute barbiturate toxicity results in CNS problems, including lethargy and coma. Constricted pupils, confusion, hypotension, poor coordination, respiratory depression, and coma may be found on physical exams. Although a barbiturate serum level may be obtained, the clinical presentation predicts the seriousness of the overdose. Attention must be given to the ABC's - airway, breathing and circulation. Gastric Lavage and multiple doses of activated charcoal may be used to decontaminate the GI system. IV fluids and forced diuresis and alkalinization should be used for long acting barbiturate intoxication. In severe cases, hemodialysis may be necessary. Early deaths are usually a result of shock or cardiopulmonary arrest. Later deaths are usually the result of pulmonary complications such as aspiration pneumonia or pulmonary edema.

Famous users

- Ryunosuke Akutagawa - the renowned Japanese writer who wrote Rashomon , committed suicide by overdosing on barbiturates on July 24, 1927.
 Judy Garland died from an accidental barbiturate overdose
 Marilyn Monroe also died from an overdose of barbiturates, as did George Sanders, Kenneth Williams (although an open verdict was recorded) and Jean Seberg.
 Michael Rabin, one of the most prodigious violinists America has ever had,

became dependent on barbiturates and his death was partially linked to abuse of these drugs.

Jimi Hendrix's death was a combination of barbiturate overdose and vomit inhalation.

Edie Sedgwick died in 1971 of barbiturate overdose. Death was said to be accidental/suicidal.

Tim Buckley, singer-songwriter and father of Jeff Buckley, died from an accidental overdose of heroin, alcohol, and barbiturates.

Ruan Lingyu committed suicide by overdosing on barbiturates on March 8, 1935.

Johnny Cash abused barbiturates during the height of his career.

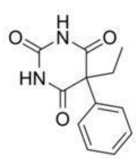
Elvis Presley used barbiturates in the last years of his life, but whether this contributed to his death is disputed.

Margaux Hemingway died from an overdose of phenobarbital.

Dorothy Kilgallen died in 1965 of an alcohol and seconal overdose. It is unclear whether the overdose was accidental or murder.

Diane Arbus committed suicide in 1971 by taking barbiturates and slitting open her wrists.

Phenobarbital



Systematic (IUPAC) name

5-ethyl-5-phenyl-1,3-diazinane-2,4,6-trione

Identifiers

CAS number 50-06-6

ATC code N05**CA24** N03**AA02**

PubChem 4763

DrugBank APRD00184

Chemical data

Formula $C_{12}H_{12}N_2O_3$

Mol. weight 232.235 g/mol

Pharmacokinetic data

Bioavailability **>95%**

Protein binding 20 to 45%

Metabolism Hepatic (mostly CYP2C19)

Half life 53 to 118 hours

Excretion Renal and fecal

Therapeutic considerations

Pregnancy cat. $D_{(US)}$

Legal status Class B(UK) Schedule IV(US)

Routes Oral, rectal, parenteral (intramuscular and intravenous)

Phenobarbital (INN) or *phenobarbitone* (former BAN) is a barbiturate, first marketed as *Luminal*® by Farbwerke Fr. Bayer and Co. It is the most widely used anticonvulsant worldwide and the oldest still in use. It also has sedative and hypnotic properties but, as with other barbiturates, has been superseded by the benzodiazepines for these indications. The World Health Organization recommends its use as first-line for partial and generalized tonic–clonic seizures in developing countries. It is a core medicine in the WHO Model List of Essential Medicines, which is a list of minimum medical needs for a basic health care system.[1] In more affluent countries, it is no longer recommended as a first or second-line choice anticonvulsant for most seizure types,[2][3] though it is still commonly used to treat neonatal seizures.[4]

History

The first barbiturate drug, barbital, was synthesized in 1902 by German chemists Emil Fischer and Joseph von Mering at Bayer. By 1904 several related drugs, including phenobarbital, had been synthesized by Fischer. Phenobarbital was brought to market in 1912 by the drug company Bayer using the brand Luminal. It remained a commonly prescribed sedative and hypnotic until the introduction of benzodiazepines in the 1950s.[5]

Phenobarbital's soporific, sedative and hypnotic properties were well known in 1912, but nobody knew it was also an effective anticonvulsant. The young doctor Alfred Hauptmann gave it to his epilepsy patients as a tranquiliser and discovered that their epileptic attacks were susceptible to the drug. Hauptmann performed a careful study of his patients over an extended period. Most of these patients were using the only effective drug then available, bromide, which had terrible side effects and limited efficacy. On

phenobarbital, their epilepsy was much improved: the worse patients suffered fewer and lighter seizures and some patients became seizure free. In addition, they improved physically and mentally as bromides were removed from their regime. Patients who had been institutionalised due to the severity of their epilepsy were able to leave and, in some cases, resume employment. Hauptman dismissed concerns that its effectiveness in stalling epileptic attacks could lead to patients suffering a build-up that needed to be "discharged". As he expected, withdrawal of the drug lead to an increase in seizure frequency – it was not a cure. The drug was quickly adopted as the first widely effective anticonvulsant, though World War I delayed its introduction in the U.S.[6]

Phenobarbital was used to treat neonatal jaundice by increasing liver metabolism and thus lowering bilirubin levels. In the 1950s, phototherapy was discovered, and became the standard treatment.[7]

In 1940, Winthrop Chemical produced sulfathiazole tablets that were contaminated with phenobarbital. This occurred because both tablets were produced side-by-side and equipment could be interchanged. Each antibacterial tablet contained more than twice the required dose of phenobarbital necessary to induce sleep. Hundreds of patients died or were injured as a result. A U.S. Food and Drug Administration investigation was highly critical of Winthrop and the scandal lead to the introduction of Good Manufacturing Practice for drugs.[7]

Phenobarbital was used for over 25 years as prophylaxis in the treatment of febrile seizures.[8] Although an effective treatment in preventing recurrent febrile seizures, it had no positive effect on patient outcome or risk of developing epilepsy. The treatment of simple febrile seizures with anticonvulsant prophylaxis is no longer recommended.[9][10]

Indications

Phenobarbital is indicated in the treatment of all types of seizures except absence seizures.[2][11] Phenobarbital is no less effective at seizure control than more modern drugs such as phenytoin and carbamazepine. It is, however, significantly less well tolerated.[12][13]

The first line drugs for treatment of status epilepticus are fast acting benzodiazepines such as diazepam or lorazepam. If these fail then phenytoin may be used, with phenobarbital being an alterntive in the US but used only third line in the UK.[14] Failing that, the only treatment is anaesthesia in intensive care.[11][15]

Phenobarbital is the first line choice for the treatment of neonatal seizures.[4][16][17] Concerns that neonatal seizures in themselves could be harmful make most physicians treat them aggressively. There is, however, no reliable evidence to support this approach.[18]

Side effects

Sedation and hypnosis are the principal side effects of this drug. CNs effects like dizziness, nystagmus and ataxia are also common. In old aged patients, they cause excitement and confusion while in children, they cause paradoxical hyperreactivity.

Contraindications

Acute intermittent porphyria, oversensitivity for barbiturates, prior dependence on barbiturates, severe respiratory insufficiency and hyperkinesia in children.

Overdose

Poisoning by barbiturates

Classifications and external resources

ICD-10

T42.3

eMedicine

med/207

Phenobarbital causes a "depression" of the body's systems, mainly the central and peripheral nervous systems; thus, the main characteristic of phenobarbital overdose is a "slowing" of bodily functions, including decreased consciousness (even coma), bradycardia, bradypnea, hypothermia, and hypotension (in massive overdoses). Overdose may also lead to pulmonary edema and acute renal failure as a result of shock.

The electroencephalogram of a person with phenobarbital overdose may show a marked decrease in electrical activity, to the point of mimicking brain death. This is due to profound depression of the central nervous system, and is usually reversible.[19]

Treatment of phenobarbital overdose is supportive, and consists mainly in the maintenance of airway patency (through endotracheal intubation and mechanical ventilation), correction of bradycardia and hypotension (with intravenous fluids and vasopressors, if necessary) and removal of as much drug as possible from the body. Depending on how much time has elapsed since ingestion of the drug, this may be accomplished through gastric lavage (stomach pumping) or use of activated charcoal. Hemodialysis is effective in removing phenobarbital from the body, and may reduce its half-life by up to 90%.[19] There is no specific antidote for barbiturate poisoning.

Pharmacokinetics

Phenobarbital has an oral bioavailability of approximately 90%. Peak plasma concentrations are reached 8 to 12 hours after oral administration. It is one of the longest-acting barbiturates available – it remains in the body for a very long time (half-life of 2 to 7 days) and has very low protein binding (20 to 45%). Phenobarbital is metabolized by the

liver, mainly through hydroxylation and glucuronidation, and induces most isozymes of the cytochrome P450 system. It is excreted primarily by the kidneys.

Veterinary uses

Phenobarbital is one of the initial drugs of choice to treat epilepsy in dogs, and is the initial drug of choice to treat epilepsy in cats.[20]

It may also be used to treat seizures in horses when benzodiazepine treatment has failed or is contraindicated.[21]

Heaven's Gate

The Heaven's Gate cult members committed mass suicide in 1997 with phenobarbital mixed with vodka.

Footnotes

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Benzodiazepines

The benzodiazepines(pronounced [ÌbenzYŠdajÈæzYpiÐnz], which are considered *minor tranquilizers*) are a class of drugs with sedative, hypnotic, anxiolytic, anticonvulsant, amnestic and muscle relaxant properties. Benzodiazepines are often used for short-term relief of severe, disabling anxiety or insomnia. Long-term use can be problematic due to the development of tolerance and physiological and psychological dependency. They are believed to act on the GABA receptor GABAA, the activation of which dampens higher neuronal activity. They began to be widely prescribed for stress-related ailments in the 1960s and 1970s. Their chemical structure is based upon diazepine and phenyl groups.

Pharmacology

Benzodiazepines produce their variety of effects by modulating the GABA***A*** receptor, the most prolific inhibitory receptor within the brain. The GABA***A*** receptor is made up from 5 subunits out of a possible 19, and GABA***A*** receptors made up of different combinations of subunits have different properties, different locations within the brain and importantly, different activities in regards to benzodiazepines.

In order for GABA***A*** receptors to be sensitive to the action of benzodiazepines they need to contain an ± and a ³ subunit, where the benzodiazepine binds. Once bound, the benzodiazepine locks the GABA***A*** receptor into a conformation where the neurotransmitter GABA has much higher affinity for the GABA***A*** receptor, increasing the frequency of opening of the associated Chloride ion channel and hyperpolarising the membrane. This potentiates the inhibitory effect of the available GABA leading to sedatory and anxiolytic effects. As mentioned, different benzodiazepines can have different affinities for GABA***A*** receptors made up of different collection of subunits. For instance, benzodiazepines with high activity at the ±***1*** are associated with sedation whereas those with higher affinity for GABA***A*** receptors containing ±***2*** and/or ±***3*** subunits have good anti-anxiety activity.

Members

Benzodiazepines are commonly divided into three groups: Short-acting compounds act for less than six hours and have few residual effects if taken before bedtime, but rebound insomnia may occur and they might cause wake-time anxiety. Intermediate-acting compounds have an effect for 6-10 hours, may have mild residual effects but rebound insomnia is not common. Long-acting compounds have strong sedative effects that persist. Accumulation of the compounds in the body may occur. The elimination half-life may greatly vary between individuals, especially the elderly.

The various benzodiazepines and their respective trade-names, half-lives, and primary uses are listed in the following table.

Drug Name = Common Brand Names* = Elimination Half-Life (h) [active metabolite] = Primary Effects = Approximate Equivalent Dose*****

- Alprazolam = Xanax, Xanor, Tafil, Alprox = 6-12 hours = anxiolytic = 0.5 mg
- Bromazepam = Lexotan, Lexomil, Somalium, Bromam = 10-20 hours = anxiolytic = 5-6 mg
- Chlordiazepoxide = Librium, Tropium, Risolid, Klopoxid = 5-30 hours [36-200 hours] = anxiolytic = 25 mg
- Cinolazepam = Gerodorm = 9 h = sedative = ?
- Clobazam = Frisium, Urbanol = 12-60 hours = anxiolytic, anticonvulsant = 5-20 mg
- Clonazepam = Klonopin, Klonapin, Rivotril = 18-50 hours = anxiolytic, anticonvulsant = 0.5 mg
- Clorazepate = Tranxene = [36-100 hours] = anxiolytic, anticonvulsant = 15 mg

- Diazepam = Valium, Apzepam, Stesolid, Apozepam, Hexalid, Valaxona = 20-100 hours [36-200] = anxiolytic, hypnotic, anticonvulsant, muscle relaxant = 10 mg
- Estazolam = ProSom = 10-24 h = hypnotic = 1-2 mg
- Flunitrazepam = Rohypnol, Fluscand, Flunipam, Ronal = 18-26 hours [36-200 hours] = hypnotic = 1 mg
- Flurazepam = Dalmane = [40-250 hours] = hypnotic = 15-30 mg
- Halazepam = Paxipam = [30-100 hours] = anxiolytic = 20 mg
- Ketazolam = Anxon = 2 hours = anxiolytic = 15-30 mg
- Loprazolam = Dormonoct = 6-12 hours = hypnotic = 1-2 mg
- Lorazepam = Ativan, Temesta, Lorabenz = 10-20 hours = anxiolytic = 1 mg
- Lormetazepam = Noctamid, Pronoctan = 10-12 hours = hypnotic = 1-2 mg
- Medazepam = Nobrium = 36-200 hours = anxiolytic = 10 mg
- Midazolam = Dormicum, Versed, Hypnovel = 3 hours (1.8-6 hours) = hypnotic = 5-15 mg
- Nitrazepam = Mogadon, Apodorm, Pacisyn, Dumolid = 15-38 hours = hypnotic = 10 mg
- Nordazepam = Madar, Stilny = 50-120 hours = anxiolytic = 10 mg
- Oxazepam = Serax, Serenid, Serepax, Sobril, Oxascand, Alopam, Oxabenz, Oxapax = 4-15 hours = anxiolytic = 20 mg
- Pinazepam = Domar = [40-100 hours] = sedative = 5-20 mg
- Prazepam = Centrax = [36-200 hours] = anxiolytic = 10-20 mg
- Quazepam = Doral = 25-100 hours = hypnotic = 20 mg
- Temazepam = Restoril, Normison, Euhypnos = 8-22 hours = hypnotic = 15 mg
- Tetrazepam = Mylostan = 3-26 hours = Skeletal muscle relaxant = ?
- Triazolam = Halcion, Rilamir = 2 hours = hypnotic = 0.5 mg
- DMCM = ? = ? = anxiogenic, convulsant

not used therapeutically

*Not all trade names are listed. Click on drug name to see a more conclusive list. **The duration of apparent action is usually considerably less than the half-life. With most benzodiazepines, noticeable effects usually wear off within a few hours. Nevertheless, as long as the drug is present it will exert subtle effects within the body. These effects may become apparent during continued use or may appear as withdrawal symptoms when dosage is reduced or the drug is stopped. ***Equivalent doses are based on clinical experience but may vary between individuals.[1]

Effects/Uses

Benzodiazepines are used in many situations, depending on the pharmacokinetics of each of the constituent drugs. The main use of the short-acting benzodiazepines is in insomnia, while anxiety responds better to medium- to long-acting substances that will be required all day.

Midazolam is mostly used as an intravenous injection for sedation before surgical procedures or for emergency intubation. It is commonly used in conjunction with opiates.

All benzodiazepines have the following, predictable effects, though some may be relatively stronger anxiolytics and others relatively stronger amnesics. Each effect is more likely to occur at higher doses. Selecting the right type of benzodiazepine for a particular patient and then prescribing it at the minimum effective dose will lessen the likelihood of adverse effects.

- Anxiolytic (reduce anxiety).
- Anticonvulsant (used against epileptic seizures).
- Antispasmodic (muscle relaxant).
- Sedative / hypnotic ("sleeping tablet" effect).
- Amnesic (producing anterograde amnesia).

Side effects

The side effects are predictable as they are intrinsic effects of the drug class of benzodiazepines. Knowing the relative effects of benzodiazepine types will help clinicians prescribe the most appropriate type. For example, lorazepam may not be best choice for longer term treatment in the elderly due to its stronger amnesic effects potentially aggravating forgetfulness and confusion. But then lorazepam may be a better choice for short term treatment of a younger, non-drinking patient as it is relatively less sedating.

Benzodiazepines have replaced the barbiturates because they have a lower abuse potential and relatively lower adverse reactions (chiefly, death is a relatively common result in barbiturate overdoses) and interactions. Still, drowsiness, ataxia, confusion, vertigo, impaired judgement, and a number of other effects are common.

Benzodiazepines may impair the ability to drive vehicles and to operate machinery. The impairment is worsened by consumption of alcohol, because both act as central nervous system depressants. In fact, consuming any benzodiazepine with alcohol can result in a potentially fatal overdose. The effects of long-acting benzodiazepines can also linger over to the following day.

Tolerance

Tolerance develops to many of the therapeutic effects of benzodiazepines rapidly with daily or frequent use. Generally, tolerance to the hypnotic and sedative effects occurs within days, however, tolerance to the anxiolytic effects of benzodiazepines rarely, if ever, occurs as is evidenced by a 20-year study on alprazolam (Xanax®) in the treatment of panic disorder. [2]

Dependence

Long-term benzodiazepine usage generally leads to some form of tolerance and/or dependence. It is estimated that up to 50 percent of patients prescribed diazepam for 6 months at therapeutic dosages are physically dependent. Withdrawal symptoms due to abrupt discontinuation may include:

- Insomnia

Rebound REM (or dreaming) sleep
Anxiety, possible panic attacks
Tachycardia
Hypertension
Depression, possible suicidal ideation
Tremor
Perspiration
Loss of appetite
Dysphoria

An abrupt discontinuation of benzodiazepines may result in a severe and very unpleasant withdrawal syndrome that may additionally result in:

- Convulsions

Delusions
Psychosis
Effects similar to delirium tremens

Hence, every person on long-term or high dosage of any benzodiazepine should be slowly and carefully weaned off the drug, preferably under medical supervision by a physician who is knowledgeable about the benzodiazepine withdrawal syndrome. This can usually be avoided or minimized by use of a long half-life benzodiazepine and very gradually tapering off the drug over a period of many weeks or even months.

Onset of the withdrawal syndrome from long half-life benzodiazepines might be delayed, although withdrawal from short-acting benzodiazepines often presents early.

Some of the withdrawal symptoms are identical to the symptoms for which the medication was originally prescribed. The ability to determine the difference between relapse and rebound is very important during the withdrawal phase.

Abuse Potential

Although benzodiazepines are invaluable in the treatment of anxiety disorders, they have some potential for abuse and may cause dependence or addiction. It is important to distinguish between addiction to and normal physical dependence on benzodiazepines. Intentional abusers of benzodiazepines usually have other substance abuse problems. Benzodiazepines are usually a secondary drug of abuse, used mainly to augment the high received from another drug or to offset the adverse effects of other drugs. Few cases of addiction arise from legitimate use of benzodiazepines. [3]

Intoxication

Overdosage of benzodiazepines, particularly when combined with alcohol, may lead to coma, but does not cause severe biochemical disturbances and therefore carries a relatively

good prognosis if quantities of the substances ingested are not sufficent to cause death. The antidote for all benzodiazepines is flumazenil (Annexate®), a benzodiazepine antagonist, which is occasionally used empirically in patients presenting with unexplained loss of consciousness in an emergency room setting.

Legal status

Nearly all medically-used benzodiazepines are Schedule IV in the USA under the Federal Controlled Substances Act. In Canada benzodiazepines are also Schedule IV.

Flunitrazepam (Rohypnol) is treated more severely under Federal law than other benzodiazepines. For example, despite being Schedule IV like any other benzodiazepine, it is not commercially available in the United States. It also carries tougher Federal penalties for trafficking and possession than other Schedule IV drugs. With the exception of cases involving 5 grams or more of crack, flunitrazepam is the only controlled substance in which first-offense simple possession is a federal felony. Various other countries limit the availability of benzodiazepines legally. Even though it is a commonly prescribed class of drugs, the Medicare Prescription Drug, Improvement, and Modernization Act specifically states that insurance companies that provide Medicare Part D plans are not required to cover benzodiazepines

History

The first benzodiazepine, chlordiazepoxide (Librium®) was discovered serendipitously in 1954 by the Austrian scientist Dr Leo Sternbach (1908-2005), working for the pharmaceutical company Hoffmann-La Roche. Initially, he discontinued his work on the compound Ro-5-0690, but he "rediscovered" it in 1957 when an assistant was cleaning up the laboratory. Although initially discouraged by his employer, Sternbach conducted further research that revealed the compound was a very effective tranquilizer.

In 1963 approval for use was given to diazepam (Valium®) - a simplified version of Librium - primarily to counteract anxiety symptoms. Sleep-related problems were treated with nitrazepam (Mogadon®), which was introduced in 1965 and flurazepam (Dalmane®), which was introduced in 1973.

See also

- Sedative
- Hypnotic
- Psychoactive drug

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Alprazolam

***Alprazolam* Systematic (IUPAC) name**

8-Chloro-1-methyl-6-phenyl-4H-1,2,4-triazolo(4,3-a)(1,4)benzodiazepine

Identifiers

CAS number 28981-97-7

ATC code **N05**BA12

PubChem 2118

DrugBank APRD00280

Chemical data

Formula C17H13ClN4

Mol. weight 308.8

Pharmacokinetic data

Bioavailability 80-90%

Metabolism Hepatic

Half life 6-12 hours

Excretion Renal

Therapeutic considerations

Pregnancy cat. D (USA)

Legal status Schedule IV(US)

Routes Oral

Alprazolam is a short-acting drug in the benzodiazepine class used to treat anxiety disorders and as an adjunctive treatment for depression.

Alprazolam was invented by Pfizer and is marketed under the trade name *Xanax*. Its patent expired in September 1993.

History

Alprazolam was originally marketed as an atypical benzodiazepine, but only classified as anxiety neurosis. Researchers later speculated, however, that alprazolam could be studied for serotonergic effects. On October 20, 1976, Dr. Guy Chouinard was the first to conduct a clinical trial of alprazolam in panic disorder. Patients diagnosed with panic disorder were included among participants in the study. 50 patients were given either the alprazolam or a placebo during an 8-week double-blind controlled study. Results proved that both somatic and psychic anxiety was decreased significantly in those who took the alprazolam, compared to the placebo.

Pharmacology

Alprazolam is a triazolobenzodiazepine, that is, a benzodiazepine with a triazolo-ring attached to its structure. Alprazolam binds to the GABAA subtype of the GABA receptor, increasing inhibitory effects of GABA within the central nervous system. The binding site for benzodiazepines is distinct from the binding site for barbiturates and GABA on the GABA receptor.

Unlike other benzodiazepines, alprazolam may also have some antidepressant activity, although clinical evidence of this is lacking.

Pharmacokinetics

The mechanism of action is not fully understood. Alprazolam is readily absorbed from the gastrointestinal tract. The peak plasma concentration is achieved in 1-2 hours. Most of the drug is bound to plasma protein, mainly albumin. Alprazolam is hydroxylated in the liver to ±-hydroxyalprazolam, which is also pharmacologically active. This and other metabolites are later excreted in urine as glucuronides. Some of the drug is also excreted in unchanged form.

Indications

The main medical uses for alprazolam include:

- Treatment of panic disorder, with or without agoraphobia. Alprazolam is very effective in preventing panic attacks. However, despite its efficacy, many psychiatrists are reluctant to use alprazolam for this condition because of the possibility of dependence and interdose ("breakthrough") anxiety due to its short-acting nature. An extended-release formulation of alprazolam known as Xanax XR® was introduced in 2001 and is often preferred.
- Treatment of panic attacks. Alprazolam is taken as needed (PRN); 4 to 6 doses per day are the acceptable limit. If dependence seems to develop and/or the limit is exceeded, therapy may be reconsidered and/or discontinued.

- Long-term treatment of severe anxiety disorders. Alprazolam may be used for long-term treatment of anxiety if other therapies either do not work or are contraindicated. Duration of therapy in this case is often four months or longer. The decision to use alprazolam for this purpose must be carefully made by a specialized psychiatrist, taking into account the individual's suffering, quality of life, loss of social performance and risk of dependence.
- Adjunctive treatment of depression. SSRIs (e.g.
- Other uses. Alprazolam may be used by specialists to treat severe cases of Borderline Personality Disorder. Some studies have shown positive results.

Availability

Alprazolam is generally sold in generic form in Italy and the United States. It is also sold under many other brand names, depending on the country:

- *Aceprax*® - Uruguay
- *Alplax*® - Argentina
- *Alpralid*® - Israel
- *Alprax*® - India
- *Alviz*® - Indonesia
- *Alzolam*® - India, Malaysia
- *Apo-Alpraz*® - Canada (also made by other companies under different names)
- *Apraz*® - Brazil
- *Calmax*® - Ireland
- *Constan*® - Japan
- *Frontal XR*® - (an extended release formulation) Brazil
- *Frontal*® - Brazil
- *Frontin*® - Hungary, Slovak Republic, Czech Republic
- *Helex*® - Croatia, Slovenia
- *Kalma*® - Australia
- *Kinax*® (o‰ç) - Taiwan
- *Ksalol*® - Serbia
- *Manorest*® - Sri Lanka
- *Misar*® - Croatia
- *Neurol*® - Czech Republic, Slovak Republic
- *Niravam*® - (formulation that dissolves on the tongue) United States
- *Paxal*® - Iceland
- *Prazolex*® - Romania
- *Ralozam*® - Australia
- *Restyl*® - Bahrain, Cyprus, Egypt, India, Iran, Iraq, Jordan, Kuwait, Lebanon, Libya, Oman, Qatar, Republic of Yemen, Saudi Arabia, Syria, United Arab Emirates

- *Sedipral®* - Paraguay
- *Solanax®* - Japan
- *Tafil AP®* - (an extended release formulation) Mexico
- *Tafil®* - Costa Rica, Denmark, El Salvador, Germany, Guatemala, Honduras, Mexico, Nicaragua, Panama, Venezuela
- Trankimazin® - *Spain*
- *Tranquinal®* - Ecuador, Peru
- *Xanax XR®* - (an extended release formulation) Israel [1], United States, Portugal
- *Xanax®* - Australia, Belgium, Croatia, Germany, Greece, Hungary, Ireland, Italy, Netherlands, New Zealand, Pakistan, Portugal, Switzerland, Turkey, United Kingdom, United States
- *Xanor®* - Austria, Finland, Norway, Philippines, South Africa, Sweden
- *Zamhexal®* - Australia
- *Zolarem®* - Bahrain, Benin, Burkina-Faso, Cyprus, Egypt, Ethiopia, Gambia, Ghana, Guinea, Iran, Iraq, Israel, Ivory Coast, Jordan, Kenya, Kuwait, Lebanon, Liberia, Libya, Malawi, Mali, Mauritania, Mauritius, Morocco, Niger, Nigeria, Oman, Qatar, Republic of Yemen, Saudi Arabia, Senegal, Seychelles, Sierra-Leone, South Africa, Sudan, Syria, Tanzania, Tunia, Uganda, United Arab Emirates, Zambia, Zimbabwe
- *Zoldac®* - Benin, Burkina-Faso, Ethiopia, Gambia, Ghana, Guinea, India, Ivory Coast, Kenya, Liberia, Malawi, Mali, Mauritania, Mauritius, Morocco, Niger, Nigeria, Senegal, Seychelles, Sierra-Leone, South Africa, Sudan, Tanzania, Tunia, Uganda, Zambia, Zimbabwe

Packaging

Appearance is generally as follows in the United States.

Alprazolam

Inscriptions on tablet vary depending on manufacturer.
.25 mg White oval tablet scored
.5 mg Peach oval tablet scored (.5 mg and .25 mg Alprazolam may also be found in White round tablet scored)
1 mg Blue oval scored tablet. May also be called a "football."
2 mg White rectangle multi-scored tablet. May also be called a "bar" or "stick."

Xanax XR

.5 mg White pentagonal tablet Imprinted "X /0.5"
1 mg Yellow square tablet Imprinted "X / 1"
2 mg Blue round tablet Imprinted "X / 2"
3 mg Green triangular tablet Imprinted "X / 3"

Side effects

Common side effects of alprazolam can include:

- Somnolence (drowsiness)
- Euphoria
- Confusion

Less common side effects can include:

- Fatigue
- Headache

Rare side effects can include:

- Sleep apnea

Hypoventilation (Respiratory depression)
Blurred vision
Difficulty in depth perception
Slurred speech or dysarthria
Changes in personality
Confusion
Disorientation
Amnesia (memory impairment)
Vivid dreams and/or nightmares
Jaundice
Tachycardia
Bradycardia
Changes in plasma cortisol and ACTH levels
Blood dyscrasias
Decreased salivation
Increased salivation
Diarrhea
Constipation
Nausea
Elevated hepatic (liver) enzymes
Incontinence

Rare paradoxical side effects can include:

- Nervousness
- Anxiety
- Agitation
- Rage
- Insomnia
- Muscle spasms and rigidity

Paradoxical side effects are usually a result of too high a dose (sometimes deliberate) and/or combination with alcohol. Adjusting the dosage usually causes them to cease.

Concentrations of alprazolam in cigarette smokers may be reduced up to 50% when compared to non-smokers.[3].

Long-term treatment with alprazolam may lead to physical and/or psychological dependence. Users often develop a tolerance to the drug's sedative effects, though tolerance to its anxiolytic efficacy rarely develops when used at theraputic dosage levels.

There is now a general consensus among many psychiatrists that alprazolam (a so-called 'high-potency' benzodiazepine) poses a particularly high risk for misuse, abuse and dependence. Withdrawal after long-term treatment should be done slowly over a period of weeks (or even months) to avoid serious withdrawal symptoms such as agitation, panic attacks, rebound anxiety, muscle cramps and seizures. Some patients may benefit from a substitution with diazepam or clonazepam as these drugs remain in the bloodstream longer and have a somewhat lower risk of dependency.

Patients taking a dosing regimen larger than 4mg per day have an increased potential for emotional and physical dependence. Patients who have this dependence may find it difficult to discontinue use and should seek a healthcare professional immediately so they may put you on a proper regimen to discontinue use. In addition to dependence, this medication may cause withdrawal symptoms, and in some cases has been known to cause seizures. The use of this medication may also cause a reaction called rebound anxiety. When a patient discontinues use, they may experience the symptoms they had before taking medication, but this is usually short lived. Symptoms may also be accompanied other reactions including changes in mood, anxiety or sleep. Rebound anxiety is usually a result of abrupt discontinuation of this medication; patients who taper off are less likely to experience these symptoms.

Contraindications

Use of alprazolam should be avoided in individuals with the following conditions:

- Myasthenia gravis

Acute intoxication with alcohol, narcotics, or other psychoactive substances
Ataxia
Severe hypoventilation
Acute narrow-angle glaucoma
Severe liver deficiencies (e.g. hepatitis and cirrhosis)
Severe sleep apnea
Hypersensitivity or allergy to any drug in the benzodiazepine class

Women who are pregnant should avoid alprazolam. Children of mothers who are taking alprazolam are considered at risk for withdrawal symptoms during the postnatal period. Some children born under these conditions have been reported to have neonatal flaccidity and respiratory problems. Likewise, nursing mothers should avoid alprazolam due to the fact that Benzodiazepines are known to be passed into breast milk. This can cause infants to become lethargic and loose weight. [4] [5]

Elderly individuals should be cautious in the use of alprazolam due to the possibility of increased sensitivity to side effects, especially loss of coordination and drowsiness. [6]

Eating grapefruits or drinking grapefruit juice should be avoided by those taking alprazolam.

Patients at a High Risk for Abuse and Dependence

At a particularly high risk for misuse, abuse, and dependence are:

- Patients with a history of alcohol or drug abuse and/or dependence
- Emotionally unstable patients
- Patients with severe personality disorders
- Patients with chronic pain or other physical disorders

Patients from the aforementioned group should be monitored very closely during therapy for signs of abuse and development of dependence. Discontinue therapy if any of these signs are noted. Long-term therapy in these patients is not recommended.

Recreational use

Alprazolam, like all benzodiazepines, has the potential for abuse, especially in individuals prone to addiction. Although it is not manufactured illegally, it is often diverted to the black market. The state of relaxation, anxiolysis, disinhibition and euphoria induced by benzodiazepines is the main reason for their illicit use.

Injecting alprazolam is highly dangerous. When crushed in water, it will not dissolve, potentially causing severe damage to arteries. While it is somewhat soluble in alcohol, the combination of the two, particularly when injected, can easily cause a serious (and potentially fatal) overdose. Alprazolam may also be insufflated.

Alprazolam is sometimes used with other recreational drugs to relieve the panic or distress of dysphoric reactions to psychedelics such as LSD and also to promote sleep in the "come-down" period following use of recreational drugs with stimulant or insomniac properties (such as LSD, cocaine, Amphetamine, DXM, and MDMA). It is also often used in conjunction with marijuana or heroin to potentiate the relaxing effect. It is also sometimes used by heroin addicts to suppress withdrawal symptoms.

Legal status

In the United States, alprazolam is a prescription drug and is assigned to Schedule IV of the Controlled Substances Act by the Drug Enforcement Administration. Internationally, alprazolam is included under the United Nations Convention on Psychotropic Substances.

Diazepam

Systematic (IUPAC) name

7-chloro-1-methyl-
5-phenyl-1,3-dihydro-2H-
1,4-benzodiazepin-2-one

Identifiers

CAS number 439-14-5

ATC code N05**BA01** N05**BA17**

PubChem 3016

DrugBank APRD00642

Chemical data

Formula $C_{16}H_{13}N_2ClO$

Mol. weight 284.7 g/mol

Pharmacokinetic data

Bioavailability **93%**

Metabolism Hepatic

Half life 20-100 hours

Excretion Renal

Therapeutic considerations

Pregnancy cat. $C_{(AU)}$ $D_{(US)}$

Legal status Schedule IV (International), Schedule IV (CA)

Routes Oral, IM, IV, suppository

Diazepam (IPA: [dajÈæzjpæm]), marketed under brand names *Valium*, *Stesolid*, *Seduxen*, *Bosaurin*, *Diapam*, *Antenex* and *Apozepam*)[1] is a drug which is a benzodiazepine derivative. It possesses anxiolytic, anticonvulsant, sedative, skeletal muscle relaxant and amnestic properties. This makes it a useful drug for treating anxiety, insomnia, seizures, alcohol withdrawal, and muscle spasms. It is also used before certain medical procedures (such as endoscopies) to reduce tension and anxiety, and in some surgical procedures to induce amnesia.[2][3]

Diazepam is a core medicine in the World Health Organization's "Essential Drugs List", which is a list of minimum medical needs for a basic health care system.[4] Diazepam is used to treat a wide range of conditions and is one of the most frequently prescribed benzodiazepines.

Benzodiazepine

Diazepam is a benzodiazepine that binds to a specific subunit on the GABA*A* receptor at a site that is distinct from the endogenous GABA molecule.[5][6]The GABA*A* receptor is an inhibitory channel which, when activated, decreases neurologic activity.

Due to the role of diazepam as a positive allosteric modulator of GABA, when it binds to benzodiazepine receptors it causes inhibitory effects. This arises from the hyperpolarization of the postsynaptic membrane, due to the control exerted over negative chloride ions by GABA*A* receptors.[5][7]

Diazepam appears to act on areas of the limbic system, thalamus and hypothalamus, inducing anxiolytic effects. Its actions are due to the enhancement of GABA activity.[2][5]

History

Diazepam was the second benzodiazepine to be invented by Leo Sternbach of Hoffmann-La Roche, and was approved for use in 1963. It is five times more potent than its predecessor, chlordiazepoxide, which it quickly surpassed in terms of sales. After this initial success, other pharmaceutical companies began to introduce other benzodiazepine derivatives.[8]

The benzodiazepines gained popularity among medical professionals as an improvement upon barbiturates, which have a comparatively narrow therapeutic index, and are far more sedating at therapeutic doses. The benzodiazepines are also far less dangerous; death rarely results from diazepam overdose, except in cases where it is consumed with large amounts of other depressants (such as alcohol or other sedatives).[9]

Diazepam was the top-selling pharmaceutical in the United States from 1969 to 1982, with peak sales in 1978 of 2.3 billion pills.[8] In 1966, The Rolling Stones released the song "Mother's Little Helper", which is about a mother needing the "little yellow pill" to get through the day.[10]

Over the years, physicians, psychiatrists and neurologists have discovered many new off-label uses for diazepam, such as treatment of spastic paresis and palliative treatment of stiff-person syndrome.[11] Diazepam is also found in nature. Several plants, such as potato and wheat, contain trace amounts of naturally occurring diazepam and other benzodiazepines.[12]

Pharmacokinetics

Diazepam can be administered orally, intravenously, intramuscularly, or as a suppository..[13]

When diazepam is administered orally, it is rapidly absorbed and has a fast onset of action. The onset of action is 1-5 minutes for IV administration and 15-30 minutes for IM administration. The duration of the diazepam's main pharmacological effects is 15 minutes to 1 hour for both routes of administration.[14]

Peak plasma levels are achieved 30 minutes to 2 hours after oral administration. When diazepam is administered as an intramuscular injection, absorption is slow, erratic and incomplete.[1][15]

Diazepam is highly lipid-soluble, and is widely distributed throughout the body after administration. It easily crosses both the blood-brain barrier and the placenta, and is excreted into breast milk. After absorption, diazepam is redistributed into muscle and

adipose tissue. Continual daily doses of diazepam will quickly build up to a high concentration in the body (mainly in adipose tissue), which will be far in excess of the actual dose for any given day.[13][15]

Diazepam is metabolised in the liver via the cytochrome P450 enzyme system. It has a biphasic half-life of 1-2 and 2-5 days, and has several pharmacologically active metabolites. The main active metabolite of diazepam is desmethyldiazepam (also known as nordazepam or nordiazepam). Diazepam's other active metabolites include temazepam and oxazepam. These metabolites are conjugated with glucuronide, and are excreted primarily in the urine. Because of these active metabolites, the serum values of diazepam alone are not useful in predicting the effects of the drug.[1][15]

Diazepam has a half-life (t1/2±) of 20-50 hours, and desmethyldiazepam has a half-life of 30-200 hours.[15]

Most of the drug is metabolised; very little diazepam is excreted unchanged.[13]

In humans, the protein binding of diazepam is around 98.5%.[1]

Indications

Diazepam is mainly used to treat anxiety, insomnia, and symptoms of acute alcohol or opiate withdrawal. It is also used as a premedication for inducing sedation, anxiolysis or amnesia prior to certain medical procedures (e.g. endoscopy).[1]

Diazepam is rarely used as a primary drug for the long-term treatment of epilepsy. This is due to the fact that tolerance to the anticonvulsant effects of diazepam usually develops within 6 to 12 months of treatment, effectively rendering it useless for this purpose.[13]

Diazepam has a broad spectrum of indications (most of which are off-label), including:

- Treatment of anxiety, panic attacks, and states of agitation[1]
- Treatment of status epilepticus, adjunctive treatment of other forms of epilepsy[1]
- Treatment of the symptoms of alcohol and opiate withdrawal[1]
- Short-term treatment of insomnia[1]
- Treatment of tetanus, together with other measures of intensive-treatment[16]
- Initial management of mania, together with firstline drugs like lithium, valproate or other antipsychotics
- Adjunctive treatment (with antidepressants) of depression with symptoms of anxiety
- Adjunctive treatment (with antipsychotics), in patients who develop early extrapyramidal side-effects
- Adjunctive treatment of painful muscle conditions[11]
- Adjunctive treatment of spastic muscular paresis (para-/tetraplegia) caused by cerebral or spinal cord conditions such as stroke, multiple sclerosis, spinal cord injury (long-term treatment is coupled with other rehabilitative measures)[11]
- Palliative treatment of stiff person syndrome[7]
- Pre-/postoperative sedation, anxiolysis and/or amnesia (e.g. before endoscopic or surgical procedures)[11]
- Treatment of overdosage with hallucinogens or CNS stimulants[13]
- Adjunctive treatment of drug-induced seizures, resulting from exposure to sarin,

VX, soman (or other organophosphate poisons; See CANA), lindane, chloroquine, physostigmine, or pyrethroids[13]
Emergency treatment of eclampsia, along with IV magnesium sulfate
Prophylactic treatment of oxygen toxicity during hyperbaric oxygen therapy.[17]
Used in the treatment for irritable bowel syndrome. [18]

Veterinary uses

Diazepam is used as a short term sedative and anxiolytic for cats and dogs. It is also used for short-term treatment of seizures in dogs and short-term and long-term treatment of seizures in cats. For emergent treatment of seizures, the typical dose is 0.5 mg/kg intravenously or 1-2 mg/kg per rectum of the injectable solution.[19]

Dosage

Dosages should be determined on an individual basis, depending upon the condition to be treated, the severity of symptoms, the body weight of the patient, and any comorbid conditions the patient may have.[13]

Elderly patients and those with liver disorders experience decreased metabolism of diazepam; therefore the dosage for these patients should be reduced. General guidelines for this group of patients: initial doses of 2mg to 2.5mg, 1 or 2 times daily; increase gradually as required/tolerated.[7]

Adult dosage recommendations

- Insomnia - Up to 30mg orally, as a single dose, at bedtime.[13]
- Anxiety/panic attacks - Dosage differs depending upon severity of symptoms. For panic attacks, diazepam is taken "as needed".
    - Oral - 2mg to 10mg oral, 2 to 4 times daily.[7]
    - IV/IM - 2mg to 10mg. Repeat in 3 to 4 hours, if necessary.[11]
- Pre-/postoperative sedation - If other premedications are used, they must be administered separately.[11]
    - Oral - Up to 20mg as a single dose.[13]
    - IV/IM - 2mg to 10mg, repeated at intervals of at least 5 to 10 minutes, until adequate sedation and/or anxiolysis is achieved.[13]
- Status epilepticus
    - Oral - 2mg to 10mg, 2 to 4 times daily.[7]
    - IV/IM - 5mg to 10mg. May be repeated every 5 to 10 minutes until termination of seizures. Maximum dose of 40mg to 60mg can be used; if this dose is ineffective, other anticonvulsant drug therapy should be instituted.[13]

  - Rectal solution - 10mg as a single dose. May be repeated after 5 minutes, if necessary. The oral solution can also be administered rectally.[13]
- Painful muscle conditions or muscle spasms
  - Oral - Up to 15mg daily, in divided doses. In severe spasticity associated with cerebral palsy, doses may be increased gradually up to 60mg daily.[13]
  - IV/IM - 5mg to 10mg initially, then 5mg to 10mg in 3 to 4 hours, if necessary.[11]
- Tetanus - 100 to 300µg/kg intravenously, repeated every 1 to 4 hours.[13]
- Spastic paresis - Usually starting with 3 times daily 2mg, increasing to up to 3 times 20mg in slow increments, taking care to avoid ataxia.
- Alcohol/opioid withdrawal - For symptomatic relief of agitation, tremor, delirium tremens and hallucinosis.
  - Oral - 10mg, 3 or 4 times during the first 24 hours. Reduce to 5mg, 3 or 4 times a day, or as needed.[7]
  - IV/IM - 10mg initially, 5mg to 10mg in 3 to 4 hours, if necessary.[11]
- Initial treatment of mania - 30 to 40mg daily oral or rectal, rarely more.
- Overdosage with hallucinogens/CNS stimulants - Normally a single intravenous dose of 10 to 20mg is sufficient.
- Adjunctive treatment of depression - Usually 10 to 30mg daily oral, the greater part of the dose given at bedtime. The doses should be decreased and the medication stopped as soon as the clinical situation allows.
- Adjunctive treatment of extrapyramidal side-effects - Depends on the individual. Effective dose(s) unknown. Do not administer for more than 4 weeks.[20]
- Cardioversion - To relieve anxiety/tension and to reduce recall of procedure. 5mg to 15mg IV, 5 to 10 minutes prior to the procedure.[11]
- Prophylactic treatment of oxygen toxicity during hyperbaric therapy - 5mg to 10mg.[17]

Pediatric dosage recommendations

- Patients over 6 months of age:
  - Initiate therapy with the lowest effective dose.[7]
  - Oral: Initial dose of 40 to 200µg/kg of bodyweight. Can be repeated as tolerated, up to 4 times daily.[13]
  - Rectal suppository: 40 to 200µg/kg of bodyweight, which can be repeated as tolerated up to 4 times daily.[13]
    - Sedation or muscle relaxation[13]
      - IV/IM - 200µg/kg of bodyweight.
    - Status epilepticus[13]
      - IV/IM - 200 to 300µg/kg of bodyweight. May be repeated after 5 to 10 minutes, if required.

- Rectal solution - 5mg (for patients 1 to 3 years of age); repeat after 5 to 10 minutes, if necessary.
- Tetanus[11]
  - Patients 30 days to 5 years of age - 1mg to 2mg IV/IM, slowly; repeat every 3 to 4 hours, as necessary.
  - Patients 5 years of age or older - 5mg to 10mg IV/IM, slowly; repeat every 3 to 4 hours, as necessary.
- Convulsive disorders[11]
  - Patients 30 days to 5 years of age - 0.2mg to 0.5mg IV/IM, slowly, every 2 to 5 minutes. Maximum dose of 5mg.
  - Patients 5 years of age or older - 1mg IV/IM, slowly, every 2 to 5 minutes. Maximum of dose of 10mg. Repeat in 2 to 4 hours, if necessary.

- Patients under 6 months of age:
  - Diazepam should not be given to children under 6 months of age.[7]

Availability

Diazepam is supplied in the following forms:

- For oral administration:
  - Tablets - 2mg, 5mg, 10mg[7]. Generic versions available.
  - Capsules, time-release - 15mg (marketed by Roche as *Valrelease*®)[15]
  - Liquid solution - 1mg/ml in 500ml containers and unit-dose (5mg & 10mg); 5mg/ml in 30 ml dropper bottle (marketed by Roxane as *Diazepam Intensol*®)[15]
- For parenteral administration:
  - Solution for IV/IM injection - 5mg/ml. 2ml ampoules and syringes; 1ml, 2ml, 10ml vials; 2 ml Tel-E-Ject; also contains 40% propylene glycol, 10% ethyl alcohol, 5% sodium benzoate and benzoic acid as buffers, and 1.5% benzyl alcohol as a preservative.[21][15]
- For rectal administration:
  - Solution[13]
  - Suppositories - 5mg and 10mg[22][13]
- For inhalation administration:This method uses heating diazepam to form a vapor later producing an aerosol. This allows the drug to be passed through an inhalation route during an inhalation therapy.Provided in doses 2mg-20mg either in a single inhalation or multiple small inhalations [23]

Side effects

Diazepam has a range of side effects which are common to most benzodiazepines. Most common side effects include:

- Somnolence

- Suppression of REM sleep or dreaming
- Impaired motor function
    - Impaired coordination
    - Impaired balance
    - Dizziness
- Depression

Anterograde amnesia (especially pronounced in higher doses) Reflex tachycardia[14]

Rare paradoxical side effects can include: nervousness, irritability, insomnia, muscle cramps, and in extreme cases, rage, and violence.[24][25][26] If these side effects are present, diazepam treatment should be immediately terminated.

Up to 30% of individuals treated on a long-term basis develop a form of dependence known as "low-dose-dependence". These patients do not develop a tolerance, and do not need increasingly large doses to experience the euphoric side effects of the drug.

Diazepam may impair the ability to drive vehicles or operate machinery. The impairment is worsened by consumption of alcohol, because both act as central nervous system depressants.[7]

During the course of therapy, tolerance to the sedative effects usually develops, but not to the anxiolytic and myorelaxant effects.[27]

Patients with severe attacks of apnea during sleep may suffer respiratory depression (hypoventilation) leading to respiratory arrest and death.

Organic changes such as leukopenia[28] and liver-damage of the cholostatic type with or without jaundice (icterus) have been observed in a few cases.

Interactions

If diazepam is to be administered concomitantly with other drugs, attention should be paid to the possible pharmacological interactions. Particular care should be taken with drugs that enhance the effects of diazepam, such as barbiturates, phenothiazines, narcotics and antidepressants.[7]

Diazepam does not increase or decrease hepatic enzyme activity, and does not alter the metabolism of other compounds. There is no evidence which would suggest that diazepam alters its own metabolism with chronic administration.[13]

Agents which have an effect on hepatic cytochrome P450 pathways or conjugation can alter the rate of diazepam metabolism. These interactions would be expected to be most significant with long-term diazepam therapy, and their clinical significance is variable.[13]

- Diazepam increases the central depressive effects of alcohol, other hypnotics/sedatives (e.g. barbiturates), narcotics, and other muscle relaxants. The euphoriant effects of opioids may be increased, leading to increased risk of psychological dependence.[29][30]
  Cimetidine, omeprazole, ketoconazole, itraconazole, disulfiram, fluvoxamine, isoniazid, erythromycin, probenecid, propranolol, imipramine, ciprofloxacin, fluoxetine and valproic acid prolong the action of diazepam by inhibiting its elimination.[13][15]

Oral contraceptives ("the pill") significantly decrease the elimination of desmethyldiazepam, a major metabolite of diazepam.[30]
Rifampin, phenytoin, carbamazepine and phenobarbital increase the metabolism of diazepam, thus decreasing drug levels and effects.[13]
Nefazodone can cause increased blood levels of benzodiazepines.[30]
Cisapride may enhance the absorption, and therefore the sedative activity, of diazepam.[31]
Small doses of theophylline may inhibit the action of diazepam.[32]
Diazepam may block the action of levodopa (used in the treatment of Parkinson's Disease).[29]
Diazepam may alter digoxin serum concentrations.[13]
Other drugs that may have interactions with diazepam include: Antipsychotics (e.g. chlorpromazine), MAO inhibitors, ranitidine.[30]
Smoking tobacco can enhance the elimination of diazepam and decrease its action.[29]
Foods that acidify the urine can lead to faster absorption and elimination of diazepam, reducing drug levels and activity.[29]
Foods that alkalinize the urine can lead to slower absorption and elimination of diazepam, increasing drug levels and activity.[13]
There are conflicting reports as to whether food in general has any effects on the absorption and activity of orally administered diazepam.[29]

Contraindications

Use of diazepam should be avoided, when possible, in individuals with the following conditions:

- Ataxia

Severe hypoventilation
Acute narrow-angle glaucoma
Severe hepatic deficiencies (hepatitis and liver cirrhosis decrease elimination by a factor of 2)
Severe renal deficiencies (e.g. patients on dialysis)
Severe sleep apnea
Severe depression, particularly when accompanied by suicidal tendencies
Acute intoxication with alcohol, narcotics, or other psychoactive substances
Myasthenia gravis
Hypersensitivity or allergy to any drug in the benzodiazepine class

Special caution needed

- Pediatric patients
    - Less than 18 years of age - Treatment usually not indicated, except treatment of epilepsy, and pre-/postoperative treatment. The smallest possible effective dose should be used for this group of patients.[30]

  - Under 6 months of age - Safety and effectiveness have not been established; diazepam should not be given to individuals in this age group.[7][30]
- Elderly and very ill patients - Possibility that apnea and/or cardiac arrest may occur. Concomitant use of other central nervous system depressants increases this risk. The smallest possible effective dose should be used for this group of patients..[7][30][33]
- I.V. or I.M. injections in hypotensive individuals or those in shock should be administered carefully and vital signs should be monitored.[33]

Patients at a high risk for abuse and dependence

Diazepam can lead to physiological tolerance, and psychological and/or physical dependence. At a particularly high risk for diazepam misuse, abuse, and dependence are:

- Patients with a history of alcohol or drug abuse or dependence[7][34]
- Emotionally unstable patients
- Patients with severe personality disorders, such as Borderline Personality Disorder[35]
- Patients with chronic pain or other physical disorders

Patients from the aforementioned groups should be monitored very closely during therapy for signs of abuse and development of dependence. Discontinue therapy if any of these signs are noted. Long-term therapy in these patients is not recommended.[7][34] The American Society of Addiction Medicine has policy indicating that patients with addictive disease should not be presecribed benzodiazepines such as diazepam.

Withdrawal

Administration of therapeutic doses of diazepam for 6 weeks or longer can result in physical dependence, characterized by a withdrawal syndrome when the drug is discontinued. With larger doses, physical dependence develops more rapidly.[13]

After continued therapy in excess of a few weeks, diazepam should never be stopped abruptly. The dose should instead be lowered gradually, over a period of 2 to 4 weeks, in order to minimize withdrawal symptoms.[13][34]

Withdrawal symptoms are initially minimal, and increase in severity over the first 5 to 9 days after ingestion of the drug is stopped. Diazepam's long half-life and active metabolites delay the onset of such symptoms.[13]

The withdrawal symptoms for diazepam are similar to those of other CNS depressants (e.g. alcohol, barbiturates), and can include[13]:

- Anxiety
- Dysphoria
- Irritability
- Insomnia
- REM Rebound

- Confusion
- Tremors
- Muscle spasms
- Abdominal and muscle cramps
- Anorexia (i.e. lack of appetite)
- Nausea/vomiting
- Hyperthermia/sweating
- Hypotension

In severe cases of diazepam withdrawal, symptoms can include:

- Convulsions (i.e. seizures)
- Death

The more severe side effects usually only develop for patients who were treated with excessive doses for extended periods of time. Usually only the milder symptoms develop in patients terminating therapeutic-level treatment after several months.[7]

Overdose

An individual who has consumed too much diazepam will display one or more of the following symptoms[7][36]:

- Somnolence/difficulty staying awake
- Mental confusion
- Hypotension
- Impaired motor functions
  - Impaired reflexes
  - Impaired coordination
  - Impaired balance
  - Dizziness
- Coma

Although not usually fatal when taken alone, a diazepam overdose is considered a medical emergency and generally requires the immediate attention of medical personnel. The antidote for an overdose of diazepam (or any other benzodiazepine) is flumazenil (Anexate®). This drug is only used in cases with severe respiratory depression or cardiovascular complications. Because flumazenil is a short-acting drug and the effects of diazepam can last for days, several doses of flumazenil may be necessary. Artificial respiration and stabilization of cardiovascular functions may also be necessary. Although not routinely indicated, activated charcoal can be used for decontamination of the stomach following a diazepam overdose. Emesis is contraindicated. Dialysis is minimally effective. Hypotension may be treated with levarterenol or metaraminol.[13][9][7][36]

The oral LD***50*** (lethal dose in 50% of the population) of diazepam is 720mg/kg in mice and 1240mg/kg in rats.[7] D. J. Greenblatt and colleagues reported in 1978 on two patients who had taken 2000 and 500 mg of diazepam, respectively, went into moderately deep comas, and were discharged within 48 hours without having experienced important complications in spite of having high concentrations of diazepam and its metabolites—

desmethyldiazepam, oxazepam, and temazepam—according to samples taken in the hospital and as follow-up.[37]

Overdoses of diazepam with alcohol and/or other depressants may be fatal.[9]

Recreational use

Generally, diazepam is not used as a recreational drug as frequently as alprazolam or flunitrazepam.

Diazepam is often found as an adulterant in heroin.[38] This may be because diazepam greatly amplifies the effects of opioids.

Sometimes diazepam is used by stimulant abusers to 'come down' and sleep and to help control the urge to binge[39] and also by users of LSD and other hallucinogens to help ease their trip without unpleasant after-effects.

Popular culture references

- The Fall's ``Roche Rumble
The Velvet Underground's ``Walk on the Wild Side
The Rolling Stones' ``Mother's Little Helper

Legal status

Internationally, diazepam is a Schedule IV drug under the Convention on Psychotropic Substances.[40]

Physical properties

Diazepam occurs as solid white or yellow crystals and has a melting point of 131.5 to 134.5°C. It is odorless, and has a slightly bitter taste. The British Pharmacopoeia lists diazepam as being very slightly soluble in water, soluble in alcohol and freely soluble in chloroform. The United States Pharmacopoeia lists diazepam as soluble 1 in 16 of ethyl alcohol, 1 in 2 of chloroform, 1 in 39 of ether, and practically insoluble in water. The pH of diazepam is neutral (i.e. 7). Diazepam has a shelf-life of 5 years for oral tablets and 3 years for IV/IM solution.[13]

Diazepam should be stored at room temperature (15°-30°C). The solution for parenteral injection should be protected from light and kept from freezing. The oral forms should be stored in air-tight containers and protected from light.[15]

Diazepam can absorb into plastic, and therefore diazepam solution is not stored in plastic bottles or syringes. It can absorb into plastic bags and tubing used for intervenous infusions. Absorption appears to be dependent on several factors such as temperature, concentration, flow rates and tube length. Diazepam should not be administered if a precipitate has formed and will not dissolve.[15]

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Flunitrazepam

Systematic (IUPAC) name

6-(2-fluorophenyl)-2-methyl-9-nitro-2,5-diazabicyclo[5.4.0]undeca-5,8,10,12-tetraen-3-one

Identifiers

CAS number 1622-62-4

ATC code N05**CD03**

PubChem 3380

DrugBank none

Chemical data

Formula C16H12FN3O3

Mol. weight 313.3

Pharmacokinetic data

Metabolism Hepatic

Half life 18-26 hours

Excretion Renal

Therapeutic considerations

Legal status Schedule III(US)

Routes Oral

Flunitrazepam (formerly marketed under the trade name *Rohypnol* in North America, pronounced ÌfluĐnajÈtræzYpæm) is a drug which is a benzodiazepine derivative. It has powerful sedative, anxiolytic, and skeletal muscle relaxant properties. Unfortunately, the drug can be abused as a date rape drug and is sometimes nicknamed *roofies*.

History

Flunitrazepam was first synthesized in the early 1970s by Roche and was used in hospitals when deep sedation was needed. It first entered the commercial market in Europe in 1975, and in the 1980s it began to be available in other countries.

It originally came in 1 mg, 2 mg, and 5 mg sizes, but due to its potency and potential for abuse, the higher doses were taken off the market and it is now only available in 1 mg.

Pharmacology

Like other benzodiazepines, flunitrazepam's pharmacological effects include sedation, muscle relaxation, reduction in anxiety, and prevention of convulsions. However, flunitrazepam's sedative effects are approximately 7 to 10 times more potent than diazepam. The effects of flunitrazepam appear approximately 15 to 20 minutes after oral administration, and last for approximately four to six hours. Some residual effects can persist up to 12 hours or more after administration.

Medical uses

Flunitrazepam has not been approved by the Food and Drug Administration for medical use in the United States, and is considered to be an illegal drug there. It is available only by private prescription in the United Kingdom.[1] (though Rohypnol was discontinued in 1986, Rophynol use is still present in modern culture).

In the UK it is also used in some hospitals to sedate patients undergoing colonoscopy.

Prescription in Australia is restricted.[2][3] It is used primarily for the treatment of severe insomnia that has not responded to other treatments.

Rohypnol is classified as a schedule 6 drug in South Africa.[4] It is available by prescription only, and restricted to 1 mg doses. Travelers from South Africa to the United States are limited to a 30-day supply. The drug must be declared to US Customs upon arrival. If a valid prescription cannot be produced, the drug may be subject to Customs search and seizure, and the traveler may face criminal charges or deportation.

Abuse Potential

Drug-facilitated Sexual Assault

Flunitrazepam is known to induce anterograde amnesia in sufficient doses; individuals are unable to remember certain events that they experienced while under the influence of the drug. This effect is particularly dangerous when flunitrazepam is used to aid in the commission of sexual assault; victims may not be able to clearly recall the assault, the assailant, or the events surrounding the assault.

It is difficult to estimate just how many flunitrazepam-facilitated rapes have occurred in the past. Very often, biological samples are taken from the victim at a time when the effects of the drug have already passed and only residual amounts remain in the body fluids. These

residual amounts are difficult, and sometimes impossible, to detect using standard screening assays available in the United States. If flunitrazepam exposure is to be detected at all, urine samples need to be collected within 72 hours and subjected to sensitive analytical tests. The problem is compounded by the onset of amnesia after ingestion of the drug, which causes the victim to be uncertain about the facts surrounding the rape. This uncertainty may lead to critical delays or even reluctance to report the rape and provide appropriate biological samples for testing. If a person suspects that he or she is the victim of a flunitrazepam-facilitated rape, he or she should get laboratory testing for flunitrazepam as soon as possible.

It must be noted that an inability to remember events, including sexual encounters, is not conclusive evidence of having consumed a drugged drink: Drunkenness itself causes blackouts, sleepiness, and a reduction in inhibitions. Only a timely screening for flunitrazepam can demonstrate its use.

Drug-facilitated Robbery

In the United Kingdom, the use of flunitrazepam and other "date rape" drugs has been connected to stealing from sedated victims. One expert quoted in a British tabloid estimated that up to 2,000 individuals are robbed each year after being spiked with powerful sedatives [1], making drug-assisted robbery a more common problem than drug-assisted rape.

Criminals sometimes use flunitrazepam before committing robbery as it has a calming and anti-emotive effect. This allows the criminal to perform the robbery without becoming anxious. Flunitrazepam is also known to induce anterograde amnesia making police interrogations more difficult.[5][6][7]

In a notable flunitrazepam related case, Selina Hakki was found guilty in December 2004 of using flunitrazepam to drug wealthy men and rob them of their clothes and accessories in the UK.

Recreational drug

Although flunitrazepam has become widely known in USA for its use as a date-rape drug, it is used more frequently as a recreational drug. It is used by high school and college students, rave party attendees, and heroin and cocaine users (who call a dose of flunitrazepam a "roofie") for recreational purposes, including:

- To produce profound intoxication (Kurt Cobain overdosed on a mixture of flunitrazepam and champagne several weeks before his death)
- To boost the high produced by heroin, or ease the anxiety and/or sleeplessness of withdrawal
- To counteract the side effects of stimulants (e.g. insomnia, paranoia, jitteriness)
- To "soften" the so-called "crash" which follows heavy usage of stimulants, such as cocaine or methamphetamine
- To improve sex drive and appetite.

Flunitrazepam is usually consumed orally, and is often combined with alcohol. It is also occasionally insufflated (i.e. tablets are crushed into powder and snorted). In some European

countries, there was an alcohol solution of flunitrazepam (Darkene), taken by injection, with very strong effects.

Side effects

Flunitrazepam is considered to be one of the most addictive of the benzodiazepines, along with clonazepam, midazolam, temazepam, lorazepam and alprazolam. Its use causes several notable side effects, including:

- Drowsiness
- Loss of motor control
  - Dizziness
  - Lack of coordination
- Slurred speech
- Amnesia

Confusion
Gastrointestinal disturbances, lasting 12 or more hours.
Respiratory depression in higher doses

Long-term use of flunitrazepam can result in psychological and physical dependence and the appearance of withdrawal symptoms when the drug is discontinued. Flunitrazepam impairs cognitive and psychomotor functions, affecting reaction time and driving skill. The use of this drug in combination with alcohol potentiates these side effects, and can lead to toxicity.

Legal status

Flunitrazepam is currently a Schedule III drug under the international Convention on Psychotropic Substances of 1971 [2]; in the United States, it is on Schedule IV

According to FDA Associate Director for Domestic and International Drug Control Nicholas Reuter[3]:

Flunitrazepam was "temporarily controlled in Schedule IV pursuant to a treaty obligation under the 1971 Convention on Psychotropic Substances. At the time flunitrazepam was placed temporarily in Schedule IV . . . there was no evidence of abuse or trafficking of the drug in the United States."

Rophynol is currently under consideration to be rescheduled to Schedule I, and is already considered such in the States of Florida, Idaho, Minnesota, New Hampshire, New Mexico, North Dakota, Oklahoma, and Pennsylvania.

21 U.S.C. § 841 and 21 U.S.C. § 952 provide for stiff prison terms for the possession of flunitrazepam; penalties for use or distribution include life in prison, should death or serious injury occur.

In Australia, flunitrazepam is a schedule 8 drug, along with Drug Misuse and Trafficking Act 1985.

Street Terms

Street Terms for Rohypnol:

- Circles
- Date Rape Drug
- Forget me drug
- Forget me now
- Forget me pill
- Getting roached
- La Rocha
- Lunch money drug
- Mexican valium
- Pingus
- R-2
- Reynolds
- Rib
- Roach-2
- Roapies
- Robutal
- Roofies
- Rope
- Rophies
- Row-shay
- Ruffles
- Wolfies
- Fuzzy Loving

Footnotes

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Lorazepam

Systematic (IUPAC) name

9-chloro-6-(2-chlorophenyl)-4-hydroxy-
2,5-diazabicyclo[5.4.0]undeca-
5,8,10,12-tetraen-3-one

Identifiers

CAS number 846-49-1

ATC code N05**BA06**

PubChem 3958

DrugBank APRD00116

Chemical data

Formula C15H10Cl2N2O2

Mol. weight 321.2

Pharmacokinetic data

Bioavailability **85%**

Metabolism Hepatic

Half life 10-20 hours

Excretion Renal

Therapeutic considerations

Pregnancy cat. D (USA)

Legal status Schedule IV(US)

Routes Oral, I.M., I.V., parenteral

Lorazepam (marketed under the brand names *Ativan*®, *Temesta*®, *Tavor*®) is a drug which is a benzodiazepine derivative. Pharmacologically, it is classified as a sedative-hypnotic, anxiolytic and anticonvulsant.

Trade Names: Trapax

Pharmacology and pharmacokinetics

Lorazepam is rapidly and nearly completely absorbed after any mode of application (oral, sublingual, i.m., i.v.). The onset of action is several minutes after i.v. injections, 30 to 45 minutes after oral/sublingual administration, and up to 1 hour after i.m. injections.

The duration of action depends on the dose, and is normally 6 to 12 hours. The half-life of lorazepam in patients with normal liver function is 11 to 18 hours. Therefore, 2 to 4 daily doses are often needed.

0.5mg (500μg) of lorazepam is equivalent to 5mg of diazepam [1]. Other experts estimate a proportion of 1mg lorazepam to 5mg diazepam.

Indications

Lorazepam is indicated for:

- Treatment of anxiety disorders (especially Panic Disorder)
- Short-term treatment of insomnia, particularly if associated with severe anxiety
- Treatment of symptoms associated with alcohol withdrawal
- As a premedication,
  - To facilitate unpleasant procedures, such as endoscopies and dental surgery.
  - To augment the action of the primary anaesthetic drug.
  - To produce varying degrees of anterograde amnesia for the duration of the procedure.
- Long-term treatment of otherwise resistant forms of petit mal epilepsy
- Acute therapy of status epilepticus
- Acute therapy of catatonic states alone/or with haloperidol (dangerous treatment, Lorazepam can have paradoxical effect)
- Treatment of acute delirium, preferably together with haloperidol (dangerous treatment, Lorazepam can have paradoxical effect)
- Supportive therapy of nausea/emesis frequently associated with cancer chemotherapy, usually together with firstline antiemetics like 5-HT3-antagonists
- Supportive therapy for Cyclic vomiting syndrome

Lorazepam is available in tablets and as a solution for intramuscular and intravenous injections. It is also available as a parenteral patch.

Dosage

Daily doses vary greatly, from 0.5 mg at bedtime for insomnia to 2.5 mg every 6 hours or more in the acute treatment of mania, before firstline drugs (such as lithium or valproic acid) control the situation.

Catatonia with inability to speak is very responsive and sometimes controlled with a single dose of 2 mg oral or slow i.v. injection. Catatonia may recur and treatment for some days may be necessary. Sometimes haloperidol is given concomitantly.

The control of status epilepticus requires slow i.v. injections of 2 to 4 (or even 8) mg. Patients should be closely monitored for respiratory depression and hypotensive effects.

In any case, dose requirements have to be individualized especially in the elderly and debilitated patients in whom the risk of oversedation is greater. Safety and effectiveness of lorazepam is not well determined in children under 18 years of age, but it is used to treat serial seizures. With higher doses (preferably i.v.-doses) the patient is frequently not able to recall unpleasant events (anterograde amnesia) such as therapeutic interventions (endoscopies, etc.), which is a desirable effect. But in these cases the risk is taken that a patient could later make unjustified allegations of sexual abuse during treatment due to poor recall.

After injections of lorazepam the patient should normally not be released from hospital settings without a care-giving person (parent, spouse etc.) before 24 hours have elapsed, due to incalcuable residual effects of the drug like tiredness, vertigo, hypotension etc. Also, the patient should not drive a car or handle machines for 24 hours after injection.

Disadvantages

Lorazepam, like other benzodiazepines, can cause psychological and/or physical dependence. Withdrawal symptoms similar in character to those of alcohol and barbiturates have been observed after abrupt discontinuation, therefore, a gradual taper is recommended over a period of weeks or even months, depending on the length of time it was used and the dosage taken.

The likelihood of abuse, dependence and withdrawal symptoms is substantially greater with lorazepam relative to other benzodiazepines because of its short half-life, higher potency and stronger binding to the GABA receptor complex. In this regard it behaves like alprazolam (short half-life and high potency) and clonazepam (long half-life and high potency).

Long term therapy may lead to cognitive deficits, however this is reversible upon discontinuation.

Lorazepam belongs to the Food and Drug Administration (FDA) pregnancy category D which means that it is likely to cause harm to the unborn baby, although this is very rarely seen. Lorazepam given near the time of birth may cause floppy infant syndrome and withdrawal symptoms in the infant.

In some cases there can be paradoxical effects with benzodiazepines, such as increased hostility and aggression. This is thought by some doctors to be due to disinhibition, and is therefore more likely to occur in those with preexisting personality disorders who may have less than average inhibition.

Abuse

Those with preexisting substance abuse disorders or addictive personalities are more likely to abuse medications such as lorazepam, and care should be taken when prescribing it on an outpatient basis. It is often used in an inpatient setting to assist with detox.

- Illegal use: Special data is not available but as a highly potent benzodiazepine it might be used to modulate the effects of stimulant abuse or to help with a "bad trip" caused by LSD or other hallucinogens. It can be expected that lorazepam has some street use to boost the euphoriant effects of opioids like heroin, perhaps heroin and other drugs could be "cut" with lorazepam without the knowledge of the user. The risk if used together with an opioid is respiratory depression or arrest. Its most common illegal use is simply being taken in order to "chill" from the stressors of life. Many take the drug as a "chill pill" which leads to dependency.
- Date rape drug: Lorazepam has no particular taste and could in principle be misused as a 'date rape drug' since it has strong amnesic properties relatively to other benzodiazepines. But as lorazepam has poor water solubility flunitrazepam is the more commonly used drug for this purpose. The action of lorazepam together with alcohol can be dangerous in higher amounts, causing significant central nervous system depression which manifests as unconsciousness and respiratory depression. This can lead to a coma or death.

Legal status

The patent on lorazepam held by Wyeth is expired in the United States. Generic versions of the drug are now available. Brand names include Almazine, Anxiedin, Anxira, Anzepam, Aplacasse, Aplacassee, Apo-Lorazepam, Aripax, Ativan, Azurogen, Bonatranquan, Bonton, Control, Duralozam, Efasedan, Emotion, Emotival, Kalmalin, Larpose, Laubeel, Lopam, Lorabenz, Loram, Lorans, Lorapam, Lorat, Lorax, Lorazene, Lorazep, Lorazepam, Lorazin, Lorazon, Lorenin, Loridem, Lorivan, Lorsedal, Lorzem, Lozepam, Merlit, Nervistop L, Nervistopl, NIC, Novhepar, Novolorazem, Orfidal, Punktyl, Renaquil, Rocosgen, Sedatival, Sedizepan, Sidenar, Silence, Sinestron, Somnium, Stapam, Tavor, Temesta, Titus, Tranqipam, Trapax, Trapex, Upan, Wintin, Wypax.

In 2000, the U.S. drug company Mylan agreed to pay $147 million to settle accusations by the F.T.C. that they had raised the price of generic lorazepam by 2600 percent and generic clorazepate by 3200 percent in 1998 after having obtained exclusive licensing agreements for certain ingredients.

Lorazepam is a Schedule IV drug under the Controlled Substances Act in the US and internationally under the United Nations Convention on Psychotropic Substances.

References

- "Generic-Drug Maker Agrees to Settlement In Price-Fixing Case", The New York Times, July 13, 2000

Midazolam

Systematic (IUPAC) name

8-chloro-6-(2-fluorophenyl)-1-methyl-
4H-Imidazo(1,5-a)(1,4)benzodiazepine

Identifiers

CAS number 59467-70-8

ATC code N05**CD08**

PubChem 4192

DrugBank APRD00680

Chemical data

Formula $C_{18}H_{13}N_{3}ClF$

Mol. weight 325.78

Pharmacokinetic data

Bioavailability Oral ~36%, I.M. 90%+

Metabolism Hepatic

Half life 1.8-6.4 hours

Excretion Renal

Therapeutic considerations

Pregnancy cat. C (USA), C (Aus)

Legal status Schedule IV(US)

Routes Oral, I.M., I.V., parenteral

Midazolam, (marketed under brand names *Versed*®, *Hypnovel*® and *Dormicum*®, pronounced mjÈdæzYlæm) is a drug which is a benzodiazepine derivative. It has powerful anxiolytic, amnestic, hypnotic, anticonvulsant, skeletal muscle relaxant and sedative properties. It is considered a fast-acting benzodiazepine, with a short elimination half-life.

Midazolam was first synthesized in 1976 by Fryer and Walser.

Pharmacology

Unlike other benzodiazepines such as diazepam and lorazepam, midazolam is water soluble because the imidazoline ring is open at pH under 4. However, when it is injected, the slightly alkaline (pH about 7.4) environment of the bloodstream causes the imidazoline ring to close, and it becomes much more lipid soluble, facilitating its rapid uptake into nerve tissue. This, and the fact that it has a pKa of 6.15 and is therefore predominantly un-ionised (>90%) at physiological pH, accounts for its rapid onset of action.

Metabolism is by the hepatic Cytochrome p450 enzyme 3A3/3A4. It is hydroxylated to the active metabolite 1-hydroxy-midazolam and then glucuronidated before being renally excreted.

Indications

Midazolam is frequently used (usually in combination with other agents, such as morphine) by anesthesia providers (nurse anesthetists and anesthesiologists) for sedating patients prior to surgery or other invasive medical procedures, such as endoscopy. The patient typically does not actually lose consciousness, but may lose the ability to form memories (anterograde amnesia).

Due to its high potency and fast onset of effects, it is rarely prescribed outside of hospitals. An exception is buccal midazolam, used for the rapid treatment of prolonged seizures. This is an off-label use usage of midazolam, although it has become increasingly common. When using it for this purpose, the drug is squirted slowly between the gums and the inside of the cheek, where it is absorbed directly into the blood stream.

- Intramuscular or intravenous:
  - Preoperative sedation, anxiolysis, amnesia,
  - Treatment of epileptic seizures.
- Intravenous:
  - For sedation, anxiolysis, and amnesia prior to endoscopic procedures. Often used in combination with other CNS depressants.
  - For general anesthesia, often in combination with other anesthetic agents.
- Continuous I.V. infusion:
  - For sedation of intubated patients in an intensive care setting.

Oral: Syrup formulation is often used for dental preoperative sedation for children.

Dosage

The dosing of midazolam is highly variable depending on other patient factors and other concurrently administered drugs.

- Preoperative anxiolysis: 0.5-2.5 mg.
- Endoscopy: 3-5 mg (rarely 10mg) IV, often paired with short acting opiods in moderate dosage. For example, 50mg pethidine or equivalent dosage of fentanyl (2.5-5 micrograms).
- Status epilepticus: 10mg intranasally or as buccal.

Side effects and abuse potential

Midazolam is categorized as a Schedule IV controlled substance, meaning it has low abuse potential compared to substances such as hydrocodone or oxycodone. As a benzodiazepine it shares similar side effects to other members of this drug family, however it is far less often abused given the ready availability of alternatives, and its primary use in hospital settings

only. The mild amnesia caused by this drug is a side effect commonly used for its effect as a 'pre-med' before surgery. Rapid infusion of midazolam may cause transient apnea, and occasionally, respiratory arrest.

Interactions

Midazolam is metabolized almost completely by cytochrome P450-3A4. Vmax in microsomes is reported as 850 pmol/min/mg microsomal protein. Km is reported as 3.7 uMol. Metabolism in the gut wall is reported as nearly equal to metabolism in liver by CYP3A4. Therefore, midazolam will interact with other 3A4 substrates and inhibitors. Grapefruit juice reduces intestinal 3A4 and results in less gut wall metabolism and higher plasma concentrations, which could result in overdose.

Contraindications

Hypersensitivity, acute narrow angle glaucoma, shock, hypotension, head injury, and drug or alcohol use.

Overdose

Symptoms of midazolam overdose include:

- Somnolence (difficulty staying awake)
- Mental confusion
- Hypotension
- Impaired motor functions
  - Impaired reflexes
  - Impaired coordination
  - Impaired balance
  - Dizziness
- Coma

In animal models, the oral LD_{50} of midazolam is 825 mg/kg.

Midazolam overdose is considered a medical emergency and generally requires the immediate attention of medical personnel. The antidote for an overdose of midazolam (or any other benzodiazepine) is flumazenil (Anexate®).

Legal status

Midazolam is a Schedule IV drug under the Convention on Psychotropic Substances.

Carboxamides

Carboxamides are drugs that can be used as anticonvulsants. In organic chemistry carboxamides (or amino carbonyls) are functional groups with the general structure R-CO-NH_2 with R as an organic substituent.

Two amino acids, asparagine and glutamine, have a carboxamide group in them.
The following are carboxamides:

- carbamazepine

oxcarbazepine

Gamma-aminobutyric acid

Gamma-aminobutyric acid (usually abbreviated to *GABA*) is an inhibitory neurotransmitter found in the nervous systems of widely divergent species. It is the chief inhibitory neurotransmitter in the vertebrate central nervous system.

Systematic name 4-aminobutanoic acid

Other names GABA

Molecular formula $C_4H_9NO_2$

SMILES C(CC(=O)O)CN

Molar mass 103.12 g/mol

Appearance white solid

CAS number 56-12-2

Properties

Solubility in water 0.5 M (20 °C)

Melting point 203°C (476 K)

Acidity (pK_a) 10.43

Basicity (pK_b) 9.77

Except where noted otherwise, data are given for materials in their standard state (at 25 °C, 100 kPa)

Action and receptors

In vertebrates, GABA acts at inhibitory synapses in the brain. GABA acts by binding to specific receptors in the plasma membrane of both pre- and postsynaptic neurons. This binding causes the opening of ion channels to allow either the flow of negatively-charged chloride ions into the cell or positively-charged potassium ions out of the cell. This will typically result in a negative change in the transmembrane potential, usually causing hyperpolarization.

Three general classes of GABA receptor are known. These include GABAA and GABAC ionotropic receptors, which are ion channels themselves, and GABAB metabotropic receptors, which are G protein-coupled receptors that open ion channels via intermediaries (G proteins).

Neurons that produce GABA as their output are called GABAergic neurons, and have chiefly inhibitory action at receptors in the vertebrate. Medium Spiny Cells are a typical example of inhibitory CNS GABAergic cells. GABA exhibits excitatory actions in insects, mediating muscle activation at synapses between nerves and muscle cells and also the stimulation of certain glands. GABA has also been shown to have excitatory roles in the vertebrate, most notably in the developing cortex.

Synthesis

Organisms synthesize GABA from glutamate using the enzyme L-glutamic acid decarboxylase and pyridoxal phosphate as a cofactor. It is worth noting that this involves converting the principal excitatory neurotransmitter (glutamate) into the principal inhibitory one (GABA).

Pharmacology

Drugs that act as agonists of GABA receptors (known as GABA analogues or GABAergic drugs) or increase the available amount of GABA typically have relaxing, anti-anxiety and anti-convulsive effects. Many of the substances below are known to cause short-term memory loss and retrograde amnesia.

Drugs that affect GABA receptors:

- avermectins — doramectin, selamectin, ivermectin
- barbiturates
- bicucullines
- benzodiazepines
- baclofen
- tramadol
- opiates
- cannabinoids

- carbamazepines

cyclopyrrolone derivatives — eszopiclone, zopiclone
ethanol [1] [2]

- fluoroquinolones

- gabazine (SR-95531)

gamma-hydroxybutyrate (GHB) [3]

- imidazopyridines — zaleplon, zolpidem
- muscimol

phenytoin
picrotoxin
progabide
propofol
phenibut
thujone
valproate

Drugs that affect GABA in other ways:

- tiagabine - potentiates by inhibiting uptake into neurons and glia
- vigabatrin - potentiates by inhibiting GABA-T, preventing GABA breakdown

Potassium bromide

Molecular formula KBr

Molar mass 119.01 g/mol

Appearance white solid

CAS number [7758-02-3]

Properties

Density and phase 2.75 g/cm3, solid

Solubility in water 53.5 g/100 ml (0 °C)

Solubility in ethanol 0.142 g/100 ml (25 °C)

Melting point 734 °C (1007 K)

Boiling point 1435 °C (1708 K)

Structure

Coordination geometry octahedral

Crystal structure Sodium chloride

Dipole moment 10.41 D (gas)

Related compounds

Other anions Potassium fluoride, Potassium chloride, Potassium iodide

Other cations Lithium bromide, Sodium bromide, Rubidium bromide, Caesium bromide

Except where noted otherwise, data are given for materials in their standard state (at 25 °C, 100 kPa)

Potassium bromide (KBr) is a salt, widely used as an anticonvulsant and a sedative in the late 19th and early 20th centuries. Its action is due to the bromide ion (sodium bromide is equally effective). Potassium bromide is presently used as veterinary drug, as an antiepileptic medication for dogs and cats. It is a white crystalline powder, soluble in water. In a dilute aqueous solution, potassium bromide tastes sweet, at higher concentration it tastes bitter, and when most concentrated it tastes salty to humans (these effects are due mainly to potassium ion; sodium bromide merely tastes salty at all concentrations). In high concentration potassium bromide strongly irritates the gastric mucous membrane, leading to nausea and sometimes vomiting (again this effect is typical of all soluble potassium salts).

Chemical properties

Potassium bromide is a typical ionic salt which is fully dissociated and near pH 7 in aqueous solution. It serves as a source of bromide ions- this reaction is important for the manufacture of silver bromide for photographic film:

KBr(aq) + AgNO3(aq) ’ AgBr(s) + KNO3(aq)

Aqueous bromide Br- will also form complexes when reacted with some metal halides such as copper(II) bromide:

2 KBr(aq) + CuBr2(aq) ’ K2[CuBr4](aq)

Preparation

A traditional method for the manufacture of KBr is the reaction of potassium carbonate with a bromide of iron, Fe3Br8, made by treating scrap iron under water with excess Br2:

4 K2CO3 + Fe3Br8 ’ 8 KBr + Fe3O4 + 4 CO2

Uses

Medical and Veterinary

The anticonvulsant properties of potassium bromide were first noted by Sir Charles Locock at a meeting of the Royal Medical and Chirurgical Society in 1857. Bromide can be regarded as the first effective medication for epilepsy. At the time, it was commonly thought that epilepsy was caused by masturbation. Locock noted that bromide calmed sexual excitement and thought this was responsible for his success in treating seizures. There would not be a better drug for epilepsy until phenobarbital in 1912.

Potassium bromide is used to treat epilepsy in dogs, either as first-line treatment or in addition to phenobarbital when the seizures are not adequately controlled with phenobarbital alone. Use of bromide in cats is limited because it carries a substantial risk of causing lung inflammation (pneumonitis) in this species.

Potassium bromide is not approved by the US Food and Drug Administration (FDA) for use in humans to control seizures. In Germany it continues to be approved for use as an antiepileptic drug for humans, particularly children and aldolescents. These indications include severe forms of generalized tonic-clonic seizures, early-childhood-related Grand-Mal-seizures, and also severe myoclonic seizures during childhood. Adults who have reacted positively to the drug during childhood/adolescence may continue treatment. KBr is sold under the brand name Dibro-Be mono® (RX-only). When used for proper indications it shows promising results. The drug has almost complete bioavailability and an extremely long half-life of 6 weeks. One tablet contains 850 mg of potassium bromide. Potassium bromide is not known to interfere with the absorption or excretion of any other anticonvulsant.

The therapeutic index is very small for bromide. As with other antiepileptics, sometimes even therapeutic doses give rise to intoxication. Often indistinctable from 'expected' side-effects, these include:

- Loss of appetite, nausea/emesis, lethargy, propensity to sleep during the daytime, depression, loss of concentration and memory, confusion, headache, and
- bromism (central reactions reaching from somnolence to coma, cachexia, exicosis, loss of reflexes or pathologic reflexes, clonic seizures, tremor, ataxia, loss of neural sensitivity, paresis, papillar edema of the eyes, abnormal speech, cerebral edema, frank delirium, aggressivity, psychoses)
- Acne-form dermatitis and other forms of skin disease may also be seen, as well as mucous hypersecretion in the lungs. Asthma and rhinitis may worsen. Rarely, tongue disorder, aphten, bad breath, and obstipation occur.

Optics

KBr is transparent from the near ultraviolet to long wave infrared wavelengths (0.25-25 μm). It is used for optical windows and prisms. It must be kept in a dry environment due to high solubility and hygroscopic nature. The refractive index is about 1.55 at 1.0 μm. When measuring an infrared transmission spectrum it is a common practice to mix a sample with

KBr powder and press the sample into a disk. KBr has no significant optical absorption lines in its high transmission region.

Antidotes

An *antidote* is a substance which can counteract a form of poisoning.

Sometimes, the antidote for a particular toxin is manufactured by injecting the toxin into an animal in small doses and the resulting antibodies are extracted from the animals' blood. The venom produced by some snakes, spiders, and other venomous animals is often treatable by the use of these antivenoms, although a number do lack one, and a bite or sting from such an animal often results in death.

However, some toxins have no known antidote. For example, the poison ricin, which is produced from the waste byproduct of castor oil manufacture, has no antidote, and as a result is often fatal if it enters the human body in sufficient quantities.

Ingested poisons are frequently treated by the oral administration of activated charcoal, which adsorbs the poison, and then it is flushed from the digestive tract, removing a large part of the toxin.

Poisons which are injected into the body (such as those from bites or stings from venomous animals) are usually treated by the use of a constriction band which limits the flow of lymph and/or blood to the area, thus slowing circulation of the poison around the body.

Poison and Toxic Signs

- Acetaminophen (paracetamol) poisoning is given N-acetylcysteine as the antidote.

Anticholinergic poisoning is given Physostigmine sulfate as the antidote.
Benzodiazepine poisoning is given flumazenil as the antidote.
Carbon monoxide poisoning is given oxygen as the antidote.
Anticholinesterase poisoning is given atropine sulfate and Pralidoxime chloride 2-PAM as the antidote.
Cyanide poisoning is given amyl nitrite, sodium nitrite, and thiosulfate as the antidote.
Digoxin poisoning is given anti digoxin fab fragments as the antidote.
Ethylene glycol poisoning is given ethanol or fomepizole as the antidote.
Extrapyramidal signs poisoning is given diphenhydramine hydrochloride and benztropine mesylate as the antidote.
Heavy metal poisoning is given chelators, calcium disodium edetate (EDTA), dimercaprol (BAL), penicillamine, and 2,3-dimercaptosuccinic acid (DMSA, succimer) as the antidote.
Iron poisoning is given deferoxamine mesylate as the antidote.
Isoniazid poisoning is given pyridoxine as the antidote.
Methanol poisoning is given ethanol or fomepizole as the antidote.
Methemoglobinemia poisoning is given methylene blue as the antidote.
Opioid poisoning is given naloxone hydrochloride as the antidote.

Warfarin poisoning is given vitamin K phytonadione and fresh frozen plasma as the antidote.

Poison

In the context of biology, *poisons* are substances that can cause injury, illness, or death to organisms, usually by chemical reaction or other activity on the molecular scale, when a sufficient quantity is absorbed by an organism. Paracelsus, the father of toxicology states--"Everything is poison, there is poison in everything. Only the dose makes a thing not a poison".

In medicine (particularly veterinary) and in zoology, a poison is often distinguished from a venom. Venoms are usually defined as biologic toxins that are injected to cause their effect, while poisons are generally defined as substances which are absorbed through epithelial linings such as the skin or gut.

Terminology

Some poisons are also toxins, usually referring to naturally produced substances, such as the bacterial proteins that cause tetanus and botulism. A distinction between the two terms is not always observed, even among scientists.

Animal toxins that are delivered subcutaneously (e.g. by sting or bite) are also called venom. In normal usage, a poisonous organism is one that is harmful to consume, but a venomous organism uses poison to defend itself while still alive. A single organism can be both venomous and poisonous.

The derivative forms "toxic" and "poisonous" are synonymous.

Within chemistry and physics, a poison is a substance that obstructs or inhibits a reaction, for example by binding to a catalyst.

Lay use

The phrase "poison" is often used colloquially to describe any harmful substance:

- Carcinogens, such as some artificial sweeteners, Asbestos, Benzene, Carbon tetrachloride, Dioxin, and tobacco

Mutagens, such as Ultraviolet rays (Long term exposure may cause skin cancer such as Melanoma) and other Ionizing Radiation (causes radiation sickness and cancer)

Teratogens, such as Thalidomide

Pollutants can be poisonous, or they can be non-poisonous but harmful in other ways.

Warning symbols

Poisons have been known to be symbolized by the skull and crossbones, indicating lethal potential. This is the UN standard symbol, used in the European Union. However, it can be considered a liability for marketing. In the United States, other symbols such as Mr. Yuk are replacing the skull and crossbones. Proponents of the Mr. Yuk argue that the skull-and-crossbones symbols attracts children because of its association to pirates, and assert that Mr. Yuk does not.

Chemicals with non-lethal hazards, such as corrosivity, mild toxicity and harmfulness, may be informally referred to as "poisons", but are not usually marked with the skull-and-crossbones symbol. To contrast, see also the definitions of corrosive, harmful, environmentally hazardous and irritant. The UN standard symbol for harmful and irritant substances is an 'X' on an orange background. This is applied to materials with non-lethal hazards as well as to potentially lethal materials.

Uses of poison

The uses of poisons specifically because of their toxicity is limited. Applications have been mainly for controlling pests and weeds, and for preserving building materials and food stuffs. Where possible, specific agents which are less poisonous to humans have come to be preferred, but exceptions such as phosphine continue in use.

Throughout human history, intentional application of poison has been used as a method of assassination, murder, suicide and execution. As a method of execution, poison has been ingested, as the ancient Athenians did (see Socrates), inhaled, as with carbon monoxide or hydrogen cyanide (see gas chamber), or injected (see lethal injection). Many languages describe lethal injection with their corresponding words for "poison shot".

Poisonous materials are often used for their chemical or physical properties other than being poisonous. The most effective, easiest, safest, or cheapest option for use in a chemical synthesis may be a poisonous material. Particularly in experimental laboratory syntheses a specific reactivity is used, despite the toxicity of the reagent. Chromic acid is an example of such a "simple to use" reagent. Many technical applications call for some specific physical properties; a toxic substance may possess these properties and therefore be superior. Reactivity, in particular, is important. Hydrogen fluoride, for example, is poisonous and extremely corrosive. However, it has a high affinity for silicon, which is exploited by using HF to etch glass or to manufacture silicon semiconductor chips.

Biological poisoning

Acute poisoning is exposure to a poison on one occasion or during a short period of time. Symptoms develop in close relation to the exposure.

Chronic poisoning is long-term repeated or continuous exposure to a poison where symptoms do not occur immediately or after each exposure. The patient gradually becomes ill, or becomes ill after a long latent period. Chronic poisoning most commonly occurs following exposure to poisons that bioaccumulate such as mercury and lead.

Contact or absorption of poisons can cause rapid death or impairment. Agents that act on the nervous system can paralyze in seconds or less, and include both biologically derived neurotoxins and so-called nerve gases, which may be synthesized for warfare or industry.

Inhaled or ingested cyanide as used as method of execution on US gas chambers almost instantly starves the body of energy by inhibiting the enzymes in mitochondria that make ATP. Intravenous injection of an unnaturally high concentration of potassium chloride, such as in the execution of prisoners in parts of the United States, quickly stops the heart by eliminating the cell potential necessary for muscle contraction.

Most (but not all) pesticides are created to act as poisons to target organisms, although acute or less observable chronic poisoning can also occur in non-target organism, including the humans who apply the pesticides and other beneficial organisms.

Many substances regarded as poisons are toxic only indirectly. An example is "wood alcohol" or methanol, which is not poisonous itself, but is chemically converted to toxic formaldehyde and formic acid in the liver. Many drug molecules are made toxic in the liver, and the genetic variability of certain liver enzymes makes the toxicity of many compounds differ between individuals.

The study of the symptoms, mechanisms, treatment and diagnosis of biological poisoning is known as toxicology.

Exposure to radioactive substances can produce radiation poisoning, an unrelated phenomenon.

Poisoning in humans

Children

- Poisoning is the fourth most common cause of accidental deaths in children.
- Children less than 5 years of age, as well as adolescents, are prone to poisoning.
- Accidental ingestions are most common in children less than 5 years old.
- 90% of all poisonings occur at home, the most common site being the kitchen and the bathroom.
- Unintentional poisonings occur most frequently when routines are disrupted, for example moving and vacations.
- Child safety caps have helped decrease the number of poisonings; however, they are not 100% effective and should not give a false sense of security.
- All potential poisons should be properly labeled, stored out of reach of children, and locked.
- Adolescent ingestions are more typically a result of suicidal attempts or experimentation with illicit drugs.
- Parents should receive anticipatory guidance regarding poisonings and should have the number to reach their local poison control center available, in

the USA the phone number is 1-800-222-1222. Poison control centers are free, 24 hours, and confidential.

Poisoning management

- Poison Control Centers (In the US reachable at 1-800-222-1222 at all hours) provide immediate, free, and expert treatment advice and assistance over the telephone in case of suspected exposure to poisons or toxic substances.

General first aid

- If the poison is an inhalant, remove the patient from the area and to fresh air.
- If the poisoning is affecting the skin, remove the clothing and wash the skin thoroughly unless a dry powder is the cause of the poisoning.
- If the poison is in the eye, flush the eye thoroughly for at least 15 minutes.
- Following ingestion, ensure the person remains calm, do not induce vomiting, small fluids are recommended for corrosive substances (e.g. household cleaners).
- Following these measures a poison control center can be contacted for advice on what to do next.

Initial medical management

- Initial management for all poisonings includes ensuring adequate cardiopulmonary function and providing treatment for any symptoms such as seizures, shock, and pain.

Decontamination

- The goal of gastric decontamination is to prevent absorption of the toxin. This may be achieved using activated charcoal, whole bowel irrigation, or nasogastric aspiration. Gastric lavage, cathartics, emesis, or Ipecac are no longer routinely recommended.
    - Activated charcoal is the treatment of choice to prevent absorption of the poison. It is usually administered when the patient is in the emergency room. However, charcoal is ineffective against metals, Na, K, alcohols, glycols, acids, and alkalis.

    Whole bowel irrigation cleanses the bowel, this is achieved by giving the patient large amounts of a polyethylene glycol solution. The osmotically balanced polyethylene glycol solution is not absorbed into the body, having the effect of flushing out the entire gastrointestinal tract. Its major uses are following ingestion of sustained release drugs, toxins that are not absorbed by activated charcoal (i.e. lithium, iron), and for the removal of ingested packets of drugs (body packing/smuggling).[1]

Nasogastric aspiration involves the placement of a tube via the nose down into the stomach, the stomach contents are then removed via suction. This procedure is mainly used for liquid ingestions where activated charcoal is ineffective, i.e. ethylene glycol.

Gastric lavage, commonly known as a stomach pump, is the insertion of a tube through the mouth down into the stomach, followed by administration of water or saline down the tube, the liquid is then removed again, having the overall effect of removing the contents of the stomach. Lavage has been used for many years as an initial treatment for poisoned patients, however, a recent review of the procedure for poison ingestions suggested lavage should no longer be employed routinely, if ever, in the management of poisoned patients.[2] It is still sometimes performed if it can be performed within 1 h of ingestion and the dose is potentially life threatening.

Emesis (i.e. induced by ipecac) is no longer recommended in poisoning situations.[3]

Cathartics were postulated to decrease absorption by increasing the expulsion of the poison from the gastrointestinal tract. There are two types of cathartics used in poisoned patients; saline cathartics (sodium sulfate, magnesium citrate, magnesium sulfate) and saccharide cathartics (sorbitol). They do not appear to improve patient outcome and are no longer recommended.[4]

Antidotes

Some poisons have specific antidotes:

Poison/Drug - Antidote

paracetamol - acetylcysteine

Vitamin K anticoagulants - vitamin K

opioids - naloxone

iron (and other heavy metals) - deferoxamine

benzodiazepines **- flumazenil**

ethylene glycol - ethanol or fomepizole

methanol - ethanol or fomepizole

cyanide - amyl nitrite, sodium nitrite & sodium thiosulfate

Enhanced excretion

- In some situations elimination of the poison can be enhanced using diuresis, hemodialysis, hemoperfusion, peritoneal dialysis, or exchange transfusion.

Further treatment

- In the majority of poisonings the mainstay of management is providing supportive care for the patient, i.e. treating the symptoms rather than the poison.

Types of poisons

The majority of this section is sorted by ICD-10 code, which classifies poisons based upon the nature of the poison itself. However, it is also possible to classify poisons based upon the effect the poison has (for example, "Metabolic poisons" such as Antimycin, Malonate, and 2,4-Dinitrophenol act by adversely disrupting the normal metabolism of an organism.)

(T36-T50) Poisoning by drugs, medicaments and biological substances

(T36.) Poisoning by systemic antibiotics

(T37.) Poisoning by other systemic anti-infectives and antiparasitics

(T38.) Poisoning by hormones and their synthetic substitutes and antagonists, not elsewhere classified

(T39.) Poisoning by nonopiod analgesics, antipyretics and antirheumatics

(T40.) Poisoning by narcotics and psychodysleptics (hallucinogens)

(T41.) Poisoning by anaesthetics and therapeutic gases

(T42.) Poisoning by antiepileptic, sedative-hypnotic and antiparkinsonism drugs

(T43.) Poisoning by psychotropic drugs, not elsewhere classified

(T44.) Poisoning by drugs primarily affecting the autonomic nervous system Neurotoxins interfere with nervous system functions and often lead to near-instant paralysis followed by rapid death. They include most spider and snake venoms, as well as many modern chemical weapons. One class of toxins of interest to neurochemical researchers are the various cone snail toxins known as conotoxins.

- Atropine

  - Poison hemlock

Anticholinesterases (T44.0)

  - Fasciculin

- Nerve agents

Acetylcholine antagonists

- Curare
- Pancuronium

Cell membrane disrupters Others

- Nicotine - not strictly a neurotoxin, but capable in large doses of causing heart attack

(T45.) Poisoning by primarily systemic and haematological agents, not elsewhere classified

- Phytohaemagglutinin (Red kidney bean poisoning)

(T46.) Poisoning by agents primarily affecting the cardiovascular system

- Digitoxin
- Digoxin
- Ouabain

(T47.) Poisoning by agents primarily affecting the gastrointestinal system

- Solanine

Hyoscyamine

(T48.) Poisoning by agents primarily acting on smooth and skeletal muscles and the respiratory system

- Strychnine

Aconite

(T49.) Poisoning by topical agents primarily affecting skin and mucous membrane and by ophthalmological, otorhinolaryngological and dental drugs

(T50.) Poisoning by diuretics and other unspecified drugs, medicaments and biological substances

(T51-T65) Toxic effects of substances chiefly nonmedicinal as to source

(T51.) Toxic effect of alcohol

- (T51.0) Ethanol
- (T51.1) Methanol

(T52.) Toxic effect of organic solvents

(T53.) Toxic effect of halogen derivatives of aliphatic and aromatic hydrocarbons

(T54.) Toxic effect of corrosive substances Corrosives mechanically damage biological systems on contact. Both the sensation and injury caused by contact with a corrosive resembles a burn injury.

- Acids and bases, corrosives
  - Various light metal oxides, hydroxides, superoxides
  - Bleach, some pool chemicals, other hypochlorates (acidic and oxydizing effect)
  - Hydrofluoric acid

Acids (T54.2) Strong inorganic acids, such as concentrated sulfuric acid, nitric acid or hydrochloric acid, destroy any biological tissue with which they come in contact within seconds.

Bases (T54.3) Strong inorganic bases, such as lye, gradually dissolve skin on contact but can cause serious damage to eyes or mucous membranes much more rapidly. Ammonia is a

far weaker base than lye, but has the distinction of being a gas and thus may more easily come into contact with the sensitive mucous membranes of the respiratory system. Quicklime, which has household uses, is a particularly common cause of poisoning. Some of the light metals, if handled carelessly, can not only cause thermal burns, but also produce very strongly basic solutions in sweat.

(T55.) Toxic effect of soaps and detergents

(T56.) Toxic effect of metals A common trait shared by heavy metals is the chronic nature of their toxicity (a notable exception would be bismuth, which is considered entirely non-toxic). Low levels of heavy metal salts ingested over time accumulate in the body until toxic levels are reached.

Heavy metals are generally far more toxic when ingested in the form of soluble salts than in elemental form. For example, metallic mercury passes through the human digestive tract without interaction and is commonly used in dental fillings—even though mercury salts and inhaled mercury vapor are highly toxic.

Examples:

- (T56.0) Lead poisoning
- (T56.1) Mercury
- (T56.2) Chromium
- (T56.3) Cadmium
- (T56.7) Beryllium (a highly but subtly toxic light metal)
- Antimony
- Barium
- Thallium
- Uranium

(T57.) Toxic effect of other inorganic substances

- (T57.0) Arsenic
  - Arsenic compounds
    - Arsenic trioxide

Fowler's solution

Reducing agents

- (T57.1) The most notable substance in this class is phosphorus.

(T58.) Toxic effect of carbon monoxide

- (T58) By far the most notable metabolic poison is carbon monoxide, which blocks the ability of red blood cells to transport oxygen.

(T59.) Toxic effect of other gases, fumes and vapours

- Formaldehyde (T59.2)

Phosgene

Phosphine

Hydrogen sulfide

Oxidizers Poisons of this class are generally not very harmful to higher life forms such as humans (for whom the outer layer of cells are more or less disposable), but lethal to microorganisms such as bacteria. Typical examples are ozone and chlorine (T59.4), either of which is added to nearly every municipal water supply in order to kill any harmful microorganisms present.

All halogens are strong oxidizing agents, fluorine (T59.5) being the strongest of all.
(T60.) Toxic effect of pesticides

- Pesticide poisoning

Fluoroacetate is a metabolic poison that blocks a vital step in the citric acid cycle.
Rotenone is a metabolic poison that disrupts electron transport in cellular respiration.

(T61.) Toxic effect of noxious substances eaten as seafood

- Ciguatera poisoning

Scombroid poisoning
Shellfish toxins (PSP, DSP, NSP, ASP)
Domoic acid (or Amnesic Shellfish Poison, ASP)
Tetrodotoxin

(T62.) Toxic effect of other noxious substances eaten as food

- Food poisoning

Botulin toxin
Hemlock water dropwort
Grayanotoxin (Honey intoxication)
Tetanospasmin (Tetanos Toxin)

(T63.) Toxic effect of venomous animals

- Snake and spider venoms

(T64.) Toxic effect of aflatoxin and other mycotoxin food contaminants

- Fungal toxins
  - Amanita toxin
  - Muscarine
  - Aflatoxins

(T65.) Toxic effect of other and unspecified substances

- (T65.0) Cyanide is a metabolic poison that bonds with an enzyme involved in ATP production.

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See also

- Antidote

Antihistamines

An *antihistamine* is a drug which serves to reduce or eliminate effects mediated by histamine, an endogenous chemical mediator released during allergic reactions, through action at the histamine receptor. Only agents where the main therapeutic effect is mediated by negative modulation of histamine receptors are termed antihistamines - other agents may have antihistaminergic action but are not true antihistamines.

In common use, the term antihistamine refers only to *H1-receptor antagonists*, also known as *H1-antihistamines*. It has been discovered that these H***1***-antihistamines are actually inverse agonists at the histamine H***1***-receptor, rather than antagonists per se. (Leurs, Church & Taglialatela, 2002)

Pharmacology

In allergic reactions an allergen (a type of antigen) interacts with and cross-links surface IgE antibodies on mast cells and basophils. Once the mast cell-antibody-antigen complex is formed, a complex series of events occurs that eventually leads to cell-degranulation and the release of histamine (and other chemical mediators) from the mast cell or basophil. Once released, histamine can react with local or widespread tissues through histamine receptors.

Histamine, acting on H***1***-receptors, produces pruritus, vasodilatation, hypotension, flushing, headache, tachycardia, bronchoconstriction, increases vascular permeability, potentiates pain, and more. (Simons, 2004)

While H***1***-antihistamines ameliorate these effects, they are only efficacious if administered prior to the allergen-challenge. In severe allergies, such as anaphylaxis or angioedema, these effects may be so severe as to be life-threatening.

Clinical use of antihistamines

Indications

H***1***-antihistamines are clinically used in the treatment of histamine-mediated allergic conditions. Specifically, these indications may include: (Rossi, 2004)

- allergic rhinitis
- allergic conjunctivitis
- allergic dermatological conditions (contact dermatitis)
- urticaria
- angioedema
- pruritus (atopic dermatitis, insect bites)
- anaphylactic or anaphylactoid reactions - adjunct only
- nausea and vomiting (first-generation H1-antihistamines)
- sedation (first-generation H1-antihistamines)

Antihistamines can be administered topically (through the skin, nose, or eyes) or systemically, based on the nature of the allergic condition.

Adverse drug reactions

Adverse drug reactions are most commonly associated with the first-generation H***1***-antihistamines. This is due to their relative lack of selectivity for the H***1***-receptor.

The most common adverse effect is sedation; this "side effect" is utilised in many OTC sleeping-aid preparations. Other common adverse effects in first-generation H1-antihistamines include: dizziness, tinnitus, blurred vision, euphoria, uncoordination, anxiety, insomnia, tremor, nausea and vomiting, constipation, diarrhoea, dry mouth, and dry cough. Infrequent adverse effects include: urinary retention, palpitations, hypotension, headache, hallucination, and psychosis. (Rossi, 2004)

The newer second-generation H***1***-antihistamines are far more selective for peripheral histamine H***1***-receptors and, correspondingly, have a far improved tolerability profile compared to the first-generation agents. The most common adverse effects noted for second-generation agents include: drowsiness, fatigue, headache, nausea and dry mouth. (Rossi, 2004)

First-generation H*1*-receptor antagonists

These are the oldest antihistaminergic drugs and are relatively inexpensive and widely available. They are effective in the relief of allergic symptoms, but are typically moderately to highly potent muscarinic acetylcholine receptor-antagonists (anticholinergic) agents as well. These agents also commonly have action at ±-adrenergic receptors and/or 5-HT receptors. This lack of receptor-selectivity is the basis of the poor tolerability-profile of some of these agents, especially compared with the second-generation H***1***-antihistamines. Patient response and occurrence of adverse drug reactions vary greatly between classes and between agents within classes.

The first H***1***-antihistamine discovered was piperoxan, by Forneau and Daniel Bovet (1933) in their efforts to develop a guinea pig animal-model for anaphylaxis. Bovet went on to win the 1957 Nobel Prize in Physiology or Medicine for his contribution. Following their discovery, the first-generation H***1***-antihistamines were developed in the following decades. They can be classified on the basis of chemical structure, and agents within these groups have similar properties.

Ethylenediamines

Ethylenediamines were the first group of clinically-effective H***1***-antihistamines developed.

- mepyramine (pyrilamine) antazoline

Ethanolamines

Diphenhydramine was the prototypical agent in this group. Significant anticholinergic adverse effects, including sedation, are observed in this group but the incidence of gastrointestnal adverse effects is relatively low. (Nelson, 2002; Rossi, 2004)

- diphenhydramine

carbinoxamine
doxylamine
clemastine
dimenhydrinate

Alkylamines

The isomerism is a significant factor in the activity of the agents in this group. E-triprolidine, for example, is 1000-fold more potent than Z-triprolidine. This difference relates to the positioning and fit of the molecules in the histamine H1-receptor binding site. (Nelson, 2002) Alkylamines are considered to have relatively fewer sedative and gastrointestinal adverse effects, but relatively greater incidence of paradoxical CNS stimulation. (Rossi, 2004)

- pheniramine

chlorphenamine (chlorpheniramine)
dexchlorphenamine
brompheniramine
triprolidine

Piperazines

These compounds are structurally-related to the ethylenediamines and the ethanolamines; and produce significant anticholinergic adverse effects. Compounds from this group are often used for motion sickness, vertigo, nausea and vomiting. The second-generation H***1***-antihistamine cetirizine also belongs to this chemical group. (Nelson, 2002)

- cyclizine

chlorcyclizine
hydroxyzine
meclizine

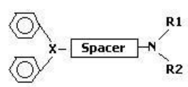
Tricyclics

These compounds differ from the phenothiazine antipsychotics in the ring-substitution and chain characteristics. (Nelson, 2002) They are also structurally-related to the tricyclic antidepressants, explaining the antihistaminergic adverse effects of those two drug classes and also the poor tolerability profile of tricyclic H***1***-antihistamines. The second-generation H***1***-antihistamine loratadine was derived from compounds in this group.

- promethazine
alimemazine (trimeprazine)
cyproheptadine
azatadine
ketotifen

Common structural features of classical antihistamine

- 2 Aromatic rings, connected to a central Carbon, Nitrogen or CO
- Spacer between the central X and the amine, usually 2-3 carbons in length, linear, ring, branched, saturated or unsaturated
- Amine is substituted with small alkyl groups eg CH3



X = N, R1 = R2 = small alkyl groups
X = C
X = CO

- Chirality at X can increase both the potency and selectivity for H1-receptors
- For maximum potency, the two aromatic rings should be orientated in different planes.
  - for example, tricyclic ring system is slightly puckered and the two aromatic rings lie in different geometrical planes, giving the drug a very high potency.

Second-generation H*1*-receptor antagonists

These are newer drugs that are much more selective for peripheral H***1*** receptors in preference to the central nervous system histaminergic and cholinergic receptors. This selectivity significantly reduces the occurrence of adverse drug reactions compared with first-generation agents, while still providing effective relief of allergic conditions.

Systemic

- acrivastine
astemizole
cetirizine
loratadine
mizolastine
terfenadine (withdrawn from most markets due to risk of cardiac arrhythmias and replaced with fexofenadine)

Topical

- azelastine
levocabastine
olopatadine

Common structural features of non-sedating antihistamines

Structure of these drugs varies from case to case. There is no common structural feature for the second generation H1-receptor antagonists.

Third-generation H*1*-receptor antagonists

These are the active enantiomer (levocetirizine) or metabolite (desloratadine & fexofenadine) derivatives of second-generation drugs intended to have increased efficacy with fewer adverse drug reactions. Indeed, fexofenadine is associated with a decreased risk of cardiac arrhythmia compared to terfenadine. However, there is little evidence for any advantage of levocetirizine or desloratadine, compared to cetirizine or loratadine respectively.

Systemic

- levocetirizine
desloratadine
fexofenadine

Other agents

Inhibitors of histamine release

These agents appear to stabilise the mast cells to prevent degranulation and mediator release.

- cromoglicate (cromolyn)
nedocromil

H_2-receptor antagonists

Main article: H2-receptor antagonist

Clinically-relevant histamine H***2***-receptors are found principally in the parietal cells of the gastric mucosa. H2-receptor "antagonists" are also inverse agonists, rather than true antagonists; and are used to reduce the secretion of gastric acid. Examples include cimetidine, ranitidine, and famotidine.

H_3- and H_4-receptor antagonists

These are experimental agents and do not yet have a defined clinical use.

H*3*-receptors antagonists

- Thioperamide

Clobenpropit

- Impromidine
  - Similar in structure to burimamide

imidazole ring

Polar moiety on the side chain - thiourea, isothiourea and guanidine

other substituents are highly variable

H*4*-receptors antagonists

- Thioperamide

Other agents with antihistaminergic activity

Many drugs, used for other indications, possess unwanted antihistaminergic activity. These include tricyclic antidepressants, antipsychotics, etc.

See also

- H2-receptor antagonist

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H2-receptor antagonists

An *H2-receptor antagonist*, often shortened to *H2 antagonist*, is a drug used to block the action of histamine on parietal cells in the stomach, decreasing acid production by these cells. These drugs are used in the treatment of dyspepsia, however their use has waned since the advent of the more effective proton pump inhibitors.

Like the H_1-antihistamines, the H***2*** antagonists are inverse agonists rather than true receptor antagonists.

History and development

Cimetidine was the prototypical histamine H2-receptor antagonist from which the later members of the class were developed. Cimetidine was the culmination of a project at Smith, Kline & French (SK&F; now GlaxoSmithKline) to develop a histamine receptor antagonist to suppress stomach acid secretion.

At the time (1964) it was known that histamine was able to stimulate the secretion of stomach acid, but also that traditional antihistamines had no effect on acid production. In the process, the SK&F scientists also proved the existence of histamine H***2*** receptors.

The SK&F team used a rational drug-design structure starting from the structure of histamine - the only design lead, since nothing was known of the then hypothetical H***2*** receptor. Hundreds of modified compounds were synthesised in an effort to develop a model of the receptor. The first breakthrough was $N_{\pm}$-guanylhistamine, a partial H***2***-receptor antagonist. From this lead the receptor model was further refined and eventually led to the development of burimamide - the first H2-receptor antagonist. Burimamide, a specific competitive antagonist at the H***2*** receptor 100-times more potent than $N_{\pm}$-guanylhistamine, proved the existence of the H***2*** receptor.

Burimamide was still insufficiently potent for oral administration and further modification of the structure, based on modifying the pKa of the compound, lead to the development of metiamide. Metiamide was an effective agent, however it was associated with unacceptable nephrotoxicity and agranulocytosis. It was proposed that the toxicity arose from the thiourea group, and similar guanidine-analogues were investigated until the ultimate discovery of Cimetidine (common brand name Tagamet).

Ranitidine (common brand name Zantac) was developed by Glaxo (also now GlaxoSmithKline) in an effort to match the success of Smith, Kline & French with cimetidine. Ranitidine was also the result of a rational drug-design process utilising the, by then, fairly refined model of the histamine H2 receptor and quantitative structure-activity relationships (QSAR).

Glaxo refined the model further by replacing the imidazole-ring of cimetidine with a furan-ring with a nitrogen-containing substituent, and in doing so developed ranitidine. Ranitidine was found to have a far-improved tolerability profile (i.e. fewer adverse drug reactions), longer-lasting action, and ten times the activity of cimetidine.

Ranitidine was introduced in 1981 and was the world's biggest-selling prescription drug by 1988. The H***2***-receptor antagonists have since largely been superseded by the even more

effective proton pump inhibitors, with omeprazole becoming the biggest-selling drug for many years.

Pharmacology

The H2 antagonists are competitive inhibitors of histamine at the parietal cell H2 receptor. They suppress the normal secretion of acid by parietal cells and the meal-stimulated secretion of acid. They accomplish this by two mechanisms: histamine released by ECL cells in the stomach is blocked from binding on parietal cell H2 receptors which stimulate acid secretion, and other substances that promote acid secretion (such as gastrin and acetylcholine) have a reduced effect on parietal cells when the H2 receptors are blocked.

Clinical use of H2-antagonists

Indications

H2-antagonists are clinically used in the treatment of acid-related gastrointestinal conditions. Specifically, these indications may include: (Rossi, 2005)

- peptic ulcer disease (PUD)

gastroesophageal reflux disease (GERD)
dyspepsia
stress ulcer prophylaxis (raniditine)

People that suffer from heartburn (GERD) infrequently may take either antacids or H2-receptor antagonists for treatment. H2-antagonists offer several advantages over antacids including longer duration of action (6–10 hours vs 1–2 hours for antacids), greater efficacy, and ability to be used prophylactically before meals to reduce the chance of heartburn occurring. Proton pump inhibitors, however, are the preferred treatment for erosive oesophagitis since they have been shown to promote healing better than H2-antagonists.

Some studies also suggest that H&sub2;-antagonists might be effective in treating herpes viruses, such as shingles and herpes simplex [1].

Adverse drug reactions

H2 antagonists are generally well-tolerated, except for cimetidine where all of the following adverse drug reactions (ADRs) are common. Infrequent ADRs include hypotension. Rare ADRs include: headache, tiredness, dizziness, confusion, diarrhoea, constipation, and rash. (Rossi, 2005) Additionally, cimetidine may also cause gynecomastia in males, loss of libido, and impotence, which are reversible upon discontinuation.

Drug interactions

With regard to pharmacokinetics, cimetidine in particular interferes with some of the body's mechanisms of drug metabolism and elimination through the liver cytochrome P450 pathway. Specifically, cimetidine is an inhibitor of the P450 enzymes CYP1A2, CYP2C9,

CYP2C19, CYP2D6, CYP2E1, and CYP3A4. By reducing the metabolism of drugs through these enzymes, cimetidine may increase their serum concentrations to toxic levels. Examples of drugs affected include: warfarin, theophylline, phenytoin, lidocaine, quinidine, propranolol, labetalol, metoprolol, tricyclic antidepressants, some benzodiazepines, dihydropyridine calcium channel blockers, sulfonylureas, metronidazole, and some recreational drugs such as ethanol and MDMA.

Examples

Cimetidine was the prototypical member of the H***2*** antagonists. Further developments, using quantitative structure-activity relationships (QSAR) led to the development of further agents with improved tolerability-profiles. In the United States, all four members of the group are available over the counter in relatively low doses, and have become extremely popular medications marketed to heartburn sufferers.

- cimetidine (Tagamet)

ranitidine (Zantac)
famotidine (Pepcid)
nizatidine (Axid, Tazac)

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Antihypertensive agents

Antihypertensives are a class of drugs that are used in medicine and pharmacology to treat hypertension (high blood pressure). There are many classes of antihypertensives, which—by varying means—act by lowering blood pressure. Evidence suggests that reduction of the blood pressure by 5-6 mmHg can decrease the risk of stroke by 40%, of coronary heart disease by 15-20%, and reduces the likelihood of dementia, heart failure, and mortality from cardiovascular disease.

Which type of medication to use initially for hypertension has been the subject of several large studies and resulting national guidelines.The fundamental goal of treatment should be the prevention of the important "endpoints" of hypertension such as heart attack, stroke and heart failure. Several classes of medications are effective in reducing blood pressure. However, these classes differ in side effect profiles, ability to prevent endpoints, and cost. The choice of more expensive agents, where cheaper ones would be equally effective, may have negative impacts on national healthcare budgets.[1]

In the United States, the JNC7 (The Seventh Report of the Joint National Committee on Prevention of Detection, Evaluation and Treatment of High Blood Pressure) recommends starting with a thiazide diuretic if single therapy is being initiated and another medication is not indicated.[2] This is based on a slightly better outcome for chlortalidone in the ALLHAT study versus other anti-hypertensives and because thiazide diuretics are relatively cheap.[3] A subsequent smaller study (ANBP2) published after the JNC7 did not show this small difference in outcome and actually showed a slightly better outcome for ACE-inhibitors in older male patients.[4]

Despite thiazides being cheap, effective, and recommended as the best first-line drug for hypertension by many experts, they are not prescribed as often as some newer drugs. Arguably, this is because they are off-patent and thus rarely promoted by the drug industry.[5]

In the United Kingdom, the June 2006 "Hypertension: management of hypertension in adults in primary care"[6] guideline of the National Institute for Health and Clinical Excellence, downgraded the role of beta-blockers due to their risk of provoking type 2 diabetes.[7]

Available drugs

Diuretics

Diuretics help the kidneys eliminate excess salt and water from the body's tissues and blood.

- Loop diuretics:
    - bumetanide
    ethacrynic acid

furosemide
torsemide

- Thiazide diuretics:
  - chlortalidone

epitizide
hydrochlorothiazide and chlorothiazide

- Thiazide-like diuretics:
  - indapamide

metolazone

- Potassium-sparing diuretics:
  - amiloride

triamterene

Although the above is a thorough list of diuretic agents, only the thiazide and thiazide-like diuretics have good evidence of beneficial effects on important endpoints of hypertension.

Antiadrenergics

Adrenergic receptor antagonists:

- Beta blockers**:**
  - atenolol

metoprolol
nadolol
oxprenolol
pindolol
propranolol
timolol

- Alpha blockers**:**
  - doxazosin

phentolamine
indoramin
phenoxybenzamine
prazosin
terazosin
tolazoline

- Mixed Alpha + Beta blockers:
  - bucindolol

carvedilol
labetalol

Although beta blockers lower blood pressure, they do not have as positive a benefit on endpoints as some other antihypertensives.[8] In particular, atenolol seems to be less useful

in hypertension than several other agents.[9] However, beta blockers have an important role in the prevention of heart attack in people who have already had a heart attack.[10]

Despite lowering blood pressure, alpha blockers have significantly poorer endpoint outcomes than other antihypertensives, and are no longer recommended as a first-line choice in the treatment of hypertension.[11] However, they may be useful for some men with symptoms of prostate disease.

Calcium channel blockers

Calcium channel blockers block the entry of calcium into muscle cells in artery walls.

- dihydropyridines:
  - amlodipine

felodipine
isradipine
nifedipine
nimodipine
nitrendipine

- non-dihydropyridines:
  - diltiazem

verapamil

ACE inhibitors

ACE inhibitors inhibit the activity of Angiotensin-converting enzyme (ACE), an enzyme responsible for the conversion of angiotensin I into angiotensin II, a potent vasoconstrictor.

- captopril

enalapril
fosinopril
lisinopril
perindopril
quinapril
ramipril
trandopril
benzapril

Angiotensin II receptor antagonists

Angiotensin II receptor antagonists work by antagonizing the activation of angiotensin receptors.

- candesartan

irbesartan
losartan
telmisartan
valsartan

Aldosterone antagonists

Aldosterone antagonists:

- spironolactone

Aldosterone antagonists are not recommended as first-line agents for blood pressure,[2] but spironolactone is useful in the treatment of heart failure.

Vasodilators

Vasodilators act directly on arteries to relax their walls so blood can move more easily through them; they are only used in medical emergencies.

- sodium nitroprusside

Centrally acting adrenergic drugs

Central alpha agonists lower blood pressure by stimulating alpha-receptors in the brain which open peripheral arteries easing blood flow. Central alpha agonists, like Clonidine, are usually prescribed when all other anti-hypertensive medications have failed.

- Clonidine

Guanabenz
Methyldopa

Adrenergic neuron blockers

- Guanethidine

Reserpine

Herbals provoking hypotension

- Agrimony

Celery
Cornsilk
Garlic
Ginger
Ginseng
Goldenseal
Hawthorn
Mistletoe
Nettle
Parsley
Pokeroot
Sage

Squill
Wild Carrot

Choice

The choice between the drugs is to a large degree determined by the characteristics of the patient being prescribed for, the drugs' side-effects, and cost. For example, asthmatics have been reported to have worsening symptoms when using beta blockers. Most drugs have other uses; sometimes the presence of other symptoms can warrant the use of one particular antihypertensive (such as beta blockers in case of tremor and nervousness, and alpha blockers in case of benign prostatic hyperplasia). The JNC 7 report outlines compelling reasons to choose one drug over the others for certain individual patients.[2]

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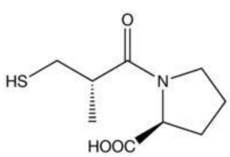
ACE inhibitors



Captopril, the first ACE inhibitor

ACE inhibitors, or inhibitors of *A*ngiotensin-*C*onverting *E*nzyme, are a group of pharmaceuticals that are used primarily in treatment of hypertension and congestive heart failure, in most cases as the drugs of first choice.

Clinical use

Indications for ACE inhibitors include:

- Prevention of cardiovascular disorders

Congestive heart failure
Hypertension
Left ventricular dysfunction
Prevention of nephropathy in diabetes mellitus

In several of these indications, ACE inhibitors are used first-line as several agents in the class have been clinically shown to be superior to other classes of drugs in the reduction of morbidity and mortality.

ACE inhibitors are often combined with diuretics in the control of hypertension (usually a thiazide), when an ACE inhibitor alone proves insufficient; and in chronic heart failure (usually furosemide) for improved symptomatic control. Thus there exists, on the market, combination products combining an ACE inhibitor with a thiazide (usually hydrochlorothiazide) in a single tablet to allow easy administration by patients.

Effects of ACE inhibitors

ACE inhibitors lower arteriolar resistance and increase venous capacitance; increase cardiac output and cardiac index, stroke work and volume, lower renovascular resistance, and lead to increased natriuresis (excretion of sodium in the urine).

Epidemiological and clinical studies have shown that ACE inhibitors reduce the progress of diabetic nephropathy independently from their blood pressure-lowering effect. This action of ACE inhibitors is utilised in the prevention of diabetic renal failure.

ACE inhibitors have been shown to be effective for indications other than hypertension even in patients with normal blood pressure. The use of a maximum dose of ACE inhibitors in such patients (including for prevention of diabetic nephropathy, congestive heart failure, prophylaxis of cardiovascular events) is justified because it improves clinical outcomes, independent of the blood pressure lowering effect of ACE inhibitors. Such therapy, of course, requires careful and gradual titration of the dose to prevent the patient suffering from the effects of rapidly decreasing their blood pressure (dizziness, fainting, etc).

Adverse effects

Common adverse drug reactions (e1% of patients) include: hypotension, cough, hyperkalemia, headache, dizziness, fatigue, nausea, renal impairment.[1]

A persistent dry cough is a relatively common adverse effect believed to be associated with the increases in bradykinin levels produced by ACE inhibitors, although the role of bradykinin in producing these symptoms remains disputed by some authors.[2] Patients who experience this cough are often switched to angiotensin II receptor antagonists.

Rash and taste disturbances, infrequent with most ACE inhibitors, are more prevalent in captopril and is attributed to its sulfhydryl moiety. This has led to decreased use of captopril in clinical setting, although it is still used in scintigraphy of the kidney.

Renal impairment is a significant adverse effect of all ACE inhibitors, and is associated with their effect on angiotensin II-mediated homeostatic functions such as renal bloodflow. ACE inhibitors can induce or exacerbate renal impairment in patients with renal artery stenosis. This is especially a problem if the patient is also concomitantly taking an NSAID and a diuretic - the so-called "triple whammy" effect - such patients are at very high risk of developing renal failure. [3]

Some patients develop angioedema due to increased bradykinin levels. There appears to be a genetic predisposition towards this adverse effect in patients who degrade bradykinin slower than average.[4]

Examples of ACE inhibitors

ACE inhibitors can be divided into three groups based on their molecular structure:

Sulfhydryl-containing ACE inhibitors

- Captopril (Capoten®), the first ACE inhibitor

Dicarboxylate-containing ACE inhibitors

This is the largest group, including:

- Enalapril (Vasotec®/Renitec®)

Ramipril (Altace®/Tritace®/Ramace®)
Quinapril (Accupril®)
Perindopril (Coversyl®)
Lisinopril (Lisodur®/Lopril®/Prinivil®/Zestril®)
Benazepril

Phosphonate-containing ACE inhibitors

- Fosinopril (Monopril®), the only member

Naturally occurring

Casokinins and lactokinins are breakdown products of casein and whey that occur naturally after ingestion of milk products, especially sour milk. Their role in blood pressure control is uncertain.[5]

Comparative information

Comparatively, all ACE inhibitors have similar antihypertensive efficacy when equivalent doses are administered. The main point-of-difference lies with captopril, the first ACE inhibitor, which has a shorter duration of action and increased incidence of certain adverse effects (cf. captopril).

Certain agents in the ACE inhibitor class have been proven, in large clinical studies, to reduce mortality post-myocardial infarction, prevent development of heart failure, etc. While these effects are likely to be class-effects, good evidence-based medicine practice would direct the use of those agents with established clinical efficacy.

Contraindications and precautions

The ACE inhibitors are contraindicated in patients with:

- Previous angioedema associated with ACE inhibitor therapy
Renal artery stenosis (bilateral, or unilateral with a solitary functioning kidney)

ACE inhibitors should be used with caution in patients with:

- Impaired renal function
Aortic valve stenosis or cardiac outflow obstruction
Hypovolaemia or dehydration
Haemodialysis with high flux polyacrylonitrile membranes

ACE inhibitors are ADEC Pregnancy category D, and should be avoided in women who are likely to become pregnant.[1] In the U.S., ACE inhibitors are required to be labelled with a "black box" warning concerning the risk of birth defects when taking during the second and third trimester. It has also been found that use of ACE inhibitors in the first trimester is also associated with a risk of major congenital malformations, particularly affecting the cardiovascular and central nervous systems.[6]

Potassium supplementation should be used with caution and under medical supervision owing to the hyperkalaemic effect of ACE inhibitors.

Angiotensin II receptor antagonists

ACE inhibitors share many common characteristics with another class of cardiovascular drugs called angiotensin II receptor antagonists, which are often used when patients are intolerant of the adverse effects produced by ACE inhibitors. ACE inhibitors do not completely prevent the formation of angiotensin II, as there are other conversion pathways, and so angiotensin II receptor antagonists may be useful because they act to prevent the action of angiotensin II at the AT***1*** receptor.

Use in combination with ACE inhibitors

While counterintuitive at first glance, the combination therapy of angiotensin II receptor antagonists with ACE inhibitors may be superior to either agent alone. This combination may increase levels of bradykinin while blocking the generation of angiotensin II and its activity at the AT***1*** receptor. This 'dual blockade' may be more effective than using an ACE inhibitor alone, because angiotensin II can be generated via non-ACE-dependent pathways. Preliminary studies suggest that this combination of pharmacologic agents may be advantageous in the treatment of essential hypertension, chronic heart failure, and nephropathy.[7][8] However, more studies are needed to confirm these highly preliminary results. While statistically significant results have been obtained for its role in treating hypertension, clinical significance may be lacking.[9]

Patients with heart failure may benefit from the combination in terms of reducing morbidity and ventricular remodeling.[10][11]

The most compelling evidence has been found for the treatment of nephropathy: this combination therapy partially reversed the proteinuria and also exhibited a renoprotective effect in patients afflicted with diabetic nephropathy, (Luno et al., 2005) and pediatric IgA nephropathy.[12]

History

The first step in the development of ACE inhibitors was the discovery of angiotensin converting enzyme (ACE) in 1956 by Leonard T. Skeggs. The importance of this enzyme in blood pressure regulation was initially underestimated. Fourteen years later, the pharmacologist Sérgio Henrique Ferreira discovered that the venom of the pit viper (Bothrops jararaca) was able to potentiate the action of bradykinin. A family of peptides, designated bradykinin potentiating factors (BPFs) was isolated from the venom and their action was linked to inhibition of bradykinin degradation by ACE.

The nonapeptide BPF teprotide (SQ 20,881) was found to have the greatest ACE inhibition potency and hypotensive effect in vivo. Teprotide had limited clinical value, however, due to its peptide nature and lack of activity when given orally. In the early 1970s, knowledge of the structure-activity relationship required for inhibition of ACE was growing. David Cushman, Miguel Ondetti and colleagues used peptide analogues to study the structure of ACE, using carboxypeptidase A as a model. Their discoveries led to the development of captopril, the first orally-active ACE inhibitor, in 1975.

Captopril was approved by the United States Food and Drug Administration in 1981. The first non-sulfhydryl-containing ACE inhibitor enalapril was marketed two years later. Since then, at least nine other ACE inhibitors have been marketed.

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Alpha blockers

Alpha blockers (also called alpha-adrenergic blocking agents) constitute a variety of drugs which block ±1-adrenergic receptors in arteries and smooth muscles.

Indications

These drugs may be used to treat:

- benign prostatic hyperplasia (BPH)
high blood pressure (hypertension). This is not typically the drug of choice unless the patient also has BPH.
symptoms of non inflammatory chronic pelvic pain syndrome, a type of prostatitis. As a side effect they may reduce blood pressure and result in lightheadedness.

Examples of alpha blockers

Alpha blockers include:

- Doxazosin (Cardura)
Prazosin (Minipress)
Phenoxybenzamine
Phentolamine (Rogitine)
Tamsulosin (Flomaxtra/Flomax)
Alfuzosin (Uroxatral)
Terazosin (Hytrin)

Tamsulosin is relatively selective for ±***1a***-adrenergic receptors, which are mainly present in the prostate. Hence, it may have a more selective action in BPH with minimal effects on blood pressure.

Adverse effects and interactions

By reducing ±***1***-adrenergic activity of the blood vessels, these drugs may cause hypotension and interrupt the baroreflex response. In doing so, they may cause dizziness, lightheadedness, or fainting when rising from a lying or sitting posture (known as orthostatic hypotension or postural hypotension). For this reason, it is generally recommended that alpha blockers should be taken at bedtime. Additionally, the risk of orthostatic hypotension may be reduced by starting at a low dose and titrating upwards as needed.

Because these medications may cause orthostatic hypotension, as well as hypotension in general, these agents may interact with other medications that increase risk for hypotension, such as other antihypertensives and vasodilators.

As discussed above, tamsulosin may have less risk for hypotension and orthostatic hypotension due to its selectivity for ±***1a***-adrenergic receptors. On the other hand, (a) shows an elevated risk for floppy iris syndrome, and (b) mighgt show ADRs characteristic of the sulfa related drugs.

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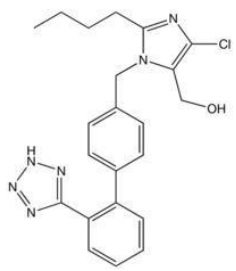
Angiotensin II receptor antagonist



Losartan, the first ARB

Angiotensin II receptor antagonists, also known as *angiotensin receptor blockers* (ARBs), *AT*1*-receptor antagonists* or *sartans*, are a group of pharmaceuticals which modulate the renin-angiotensin-aldosterone system. Their main use is in hypertension (high blood pressure), diabetic nephropathy (kidney damage due to diabetes) and congestive heart failure.

Mode of action

These substances are AT***1***-receptor antagonists – that is, they block the activation of angiotensin II AT1 receptors. Blockade of AT***1*** receptors directly causes vasodilation, reduces secretion of vasopressin, reduces production and secretion of aldosterone, amongst other actions – the combined effect of which is reduction of blood pressure.

Uses

Angiotensin II receptor antagonists are primarily used for the treatment of hypertension where the patient is intolerant of ACE inhibitor therapy. They do not inhibit the breakdown of bradykinin or other kinins, and are thus only rarely associated with the persistent dry cough that commonly limits ACE inhibitor therapy. More recently, they have been used for the treatment of heart failure in patients intolerant of ACE inhibitor therapy, particularly candesartan. Irbesartan and losartan have trial data showing benefit in hypertensive patients with type II diabetes, and may delay the progression of diabetic nephropathy.

Adverse effects

This class of drugs is usually well-tolerated, with common adverse drug reactions (ADRs) including: dizziness, headache, and/or hyperkalaemia. Infrequent ADRs associated with therapy include: first dose orthostatic hypotension, rash, diarrhoea, dyspepsia, abnormal liver function, muscle cramp, myalgia, back pain, insomnia, decreased haemoglobin levels, renal impairment, pharyngitis, and/or nasal congestion. (Rossi, 2006)

While one of the main rationales for the use of this class is the avoidance of dry cough associated with ACE inhibitor therapy, it may still rarely occur. Additionally, there is also a small risk of cross-reactivity in patients who have experienced angioedema with ACE inhibitor therapy. (Rossi, 2006)

Members

- Candesartan
Eprosartan
Irbesartan
Losartan
Olmesartan
Telmisartan
Valsartan

References

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Diuretics

A *diuretic* (colloquially called a water pill) is any drug or herb that elevates the rate of bodily urine excretion (diuresis). Diuretics also decrease the extracellular fluid (ECF) volume, and are primarily used to produce a negative extracellular fluid balance. Caffeine, cranberry juice and alcohol are all weak diuretics.

Uses

In medicine, diuretics are used to treat heart failure, liver cirrhosis, hypertension and certain kidney diseases. Diuretics alleviate the symptoms of these diseases by causing sodium and water loss through the urine. As urine is produced by the kidney, sodium and water – which cause edema related to the disease – move into the blood to replace the volume lost as urine, thereby reducing the pathological edema. Some diuretics, such as acetazolamide, help to make the urine more alkaline and are helpful in increasing excretion of substances such as aspirin in cases of overdose or poisoning.

The antihypertensive actions of some diuretics (thiazides and loop diuretics in particular) are independent of their diuretic effect. That is, the reduction in blood pressure is not due to decreased blood volume resulting from increased urine production, but occurs through other mechanisms and at lower doses than that required to produce diuresis. Indapamide was specifically designed with this is mind, and has a larger therapeutic window for hypertension (without pronounced diuresis) than most other diuretics.

Mechanism of action

Classification of common diuretics and their mechanisms of action

Agent Group = Examples = Mechanism

- = Ethanol, Water = inhibits vasopressin secretion

Acidifying salts = $CaCl_2$, NH_4Cl

Arginine vasopressin receptor 2 antagonists = amphotericin B, lithium citrate = inhibit vasopressin's action on nephron's collecting duct

Carbonic anhydrase inhibitors = acetazolamide, dorzolamide = inhibit H^+ secretion, resultant promotion of Na^+ and K^+ excretion

Loop diuretics = bumetanide, ethacrynic acid, furosemide, torsemide = inhibit the cotransporter in the medullary thick ascending limb of the loop of Henle

Osmotic diuretics = glucose, mannitol = promote osmotic diuresis

Potassium-sparing diuretics = amiloride, spironolactone, triamterene = inhibition within collecting ducts of Na^+-K^+ exchange: Spironolactone inhibits aldosterone action, Amiloride inhibits epithelial sodium channels

Thiazides = bendroflumethiazide, hydrochlorothiazide = inhibit Na^+/Cl^- reabsorption from nephrons' distal convoluted tubules

Xanthines = caffeine, theophylline = inhibit tubular reabsorption of Na^+, increase glomerular filtration rate

Chemically, diuretics are a diverse group of compounds that either stimulate or inhibit various hormones that naturally occur in the body to regulate urine production by the kidneys.

Alcohol produces diuresis through modulation of the vasopressin system.

Aldosterone

Aldosterone is a steroid hormone produced by the outer-section (zona glomerulosa) of the adrenal cortex in the adrenal gland to regulate sodium and potassium balance in the blood. It is synthesized from cholesterol by aldosterone synthase, which is absent in other sections of the adrenal gland. It is the sole endogenous member of the class of mineralocorticoids. Acting on mineralocorticoid receptors (MR) on principal cells in the distal tubule of the kidney nephron, it increases the permeability of their apical (luminal)

membrane to potassium and sodium and activates their basolateral Na+/K+ pumps, stimulating ATP hydrolysis, reabsorbing sodium (Na+) ions and water into the blood, and excreting potassium (K+) ions into the urine. Aldosterone also stimulates H+ secretion by ±-intercalated cells in the collecting duct, regulating plasma bicarbonate (HCO3) levels and its acid/base balance.[1]

Aldosterone is responsible for the reabsorption of about 2% of filtered sodium in the kidneys, which is nearly equal to the entire sodium content in human blood under normal GFR (glomerular filtration rate).[2]

Unlike neuroreceptors, classic steroid receptors are intracellularly located. The aldosterone/MR receptor complex binds on the DNA to the hormone response element, which alters protein synthesis and the transcription of messenger RNA. Some of the transcribed genes are important for transepithelial sodium transport, including serum and glucocorticoid-induced kinase, channel-inducing factor, K-ras2A, and three subunits of the epithelial sodium channel.

Aldosterone synthesis is stimulated by increased plasma angiotensin II or potassium levels, which are present in proportion to plasma sodium deficiencies. It is also stimulated by plasma acidosis. The secretion of aldosterone has a diurnal rhythm; about 75% of the daily production is secreted between 04:00 am and 10:00 am each day.[3]

Aldesterone release is also stimulated by the stretch receptors located in the atria of the heart. If decreased blood pressure is detected, the adrenal gland is stimulated by these stretch receptors to release aldesterone, which increases sodium reabsorption from the urine, sweat and the gut. This causes increased osmolarity in the extracellular fluid which will eventually return blood pressure toward normal.

Aldosterone and the kidney

Control of aldosterone release

- The role of the renin-angiotensin system

The role of sympathetic nerves
The role of baroreceptors
The role of the juxtaglomerular apparatus
The plasma concentration of potassium

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- Williams JS, Williams GH. 50th anniversary of aldosterone. J Clin Endocrinol Metab. 2003 Jun;88(6):2364-72. Full text. PMID 12788829.

Loop diuretics

Loop diuretics are diuretics that act on the ascending loop of Henle in the kidney. They are primarily used in medicine to treat hypertension and edema often due to congestive heart failure or renal insufficiency.

Mechanism of action

Loop diuretics act on the Na-K-2Cl symporter in the thick ascending limb of the loop of Henle to inhibit sodium and chloride reabsorption. Because magnesium and calcium reabsorption in the thick ascending limb is dependent on sodium and chloride concentrations, loop diuretics also inhibit their reabsorption. By disrupting the reabsorption of these ions, loop diuretics prevent the urine from becoming dilute and disrupt the generation of a hypertonic renal medulla. Without such a concentrated medulla, water has less of an osmotic driving force to leave the collecting duct system, ultimately resulting in increased urine production. This diuresis leaves less water to be reabsorbed into the blood, resulting in a decrease in blood volume.

Loop diuretics also cause vasodilation of the veins and of the kidney's blood vessels, mechanically causing a decrease in blood pressure.

The collective effects of decreased blood volume and vasodilation decrease blood pressure and ameliorate edema.

Clinical use

Loop diuretics are principally used in the following indications (Rossi, 2004):

- edema associated with heart failure, hepatic cirrhosis, renal impairment, nephrotic syndrome
- hypertension
- adjunct in cerebral/pulmonary edema where rapid diuresis is required (IV injection)

They are also sometimes used in the management of severe hypercalcemia in combination with adequate rehydration (Rossi, 2004).

Loop diuretic resistance

Renal insufficiency causes decreased bloodflow to the kidneys, which decreases the glomerular filtration rate (GFR) and reduces the ability of loop diuretics to reach their target organ, the loop of Henle. Similarly, non-steroidal anti-inflammatory drugs also decrease GFR with comparable results. In patients with reduced GFR, ceiling dosages of loop diuretics are increased proportional to the decrease in GFR. Simultaneous treatment with a thiazide diuretic such as hydrochlorothiazide (to inhibit sodium reabsorption at multiple sites in the nephron) is often successful.

Patients with congestive heart failure tend to retain sodium, also necessitating an increase in dosage. The same is true for patients with increased sodium intake.

Adverse effects

The most common adverse drug reactions (ADRs) are dose-related and relate to the effect of loop diuretics on diuresis and electrolyte balance.

Common ADRs include: hyponatremia, hypokalemia, hypomagnesemia, dehydration, hyperuricemia, gout, dizziness, postural hypotension, syncope (Rossi, 2004).

Infrequent ADRs include: dyslipidemia, increased serum creatinine concentration, hypocalcemia, rash (Rossi, 2004).

Ototoxicity (damage to the ear) is a serious, but rare ADR associated with use of loop diuretics. This may be limited to tinnitus and vertigo, but may result in deafness in serious cases.

Loop diuretics may also precipitate renal failure in patients concomitantly taking an NSAID and an ACE inhibitor -- the so-called "triple whammy" effect (Thomas, 2000).

Examples of loop diuretics

- Furosemide
- Bumetanide
- Ethacrynic acid
- Torasemide

References

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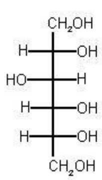
- Thomas, MC (2000). Diuretics, ACE inhibitors and NSAIDs -- the triple whammy. Med J Aust *172*, 184–185. PMID 10772593

Osmotic diuretics - Sorbitol



Chemical name Sorbitol

E number E 420

Chemical formula $C_6H_{14}O_6$

Molecular mass 182.17 g/mol

Melting point 95 °C

Boiling point 296 °C

Density 0.68 g/cm^3

CAS number [50-70-4]

SMILES OCC(O)C(O)C(O)C(O)CO

IUPAC name hexane-1,2,3,4,5,6-hexaol

Sorbitol, also known as *glucitol*, is a sugar alcohol the body metabolises slowly. It is obtained by reduction of glucose changing the aldehyde group to an additional hydroxyl group hence the name sugar alcohol.

Sorbitol is used in various cough syrups, and is usually listed under the inactive ingredients. There is a growing opinion within the medical community that it should be listed as an active ingredient, because too much Sorbitol (about 50g or more for adults) can cause severe gastro-intestinal problems.

Sorbitol is a sugar substitute often used in diet foods (including diet drinks) and sugar-free chewing gum. It also occurs naturally in many stone fruits. Sorbitol is also referred to as a nutritive sweetener because it provides calories or energy to the diet - 2.6 calories (11 kilojoules) per gram versus the average 4 calories (17 kJ) of sugar and starch, while retaining 60% of the sweetness.

Sorbitol is produced naturally by the body, yet sorbitol is poorly digested by the body. Too much sorbitol in cells can cause damage.

Diabetic retinopathy and neuropathy may be related to excess sorbitol in the cells of the eyes and nerves. The source of this sorbitol in diabetics is excess glucose, which goes through the polyol pathway. Ingesting large amounts of sorbitol can lead to some abdominal pain, gas, and mild to severe diarrhea. Sorbitol can also aggravate irritable bowel syndrome and fructose malabsorption.

Sorbitol is often used in modern cosmetics as a humectant and thickener. Some transparent gels can only be made with sorbitol as it has a refractive index sufficiently high for transparent formulations. It is also used as a humectant in some cigarettes.

Sorbitol is used as a cryoprotectant additive (mixed with sucrose and sodium polyphosphates) in the manufacture of surimi, a highly refined, uncooked fish paste most commonly produced from Alaska (or walleye) pollock (Theragra chalcogramma).

Sorbitol is identified as a potential key chemical intermediate [1] from biomass resources. Complete reduction of sorbitol opens the way to alkanes such as hexane which can be used as a biofuel. Sorbitol itself provides much of the hydrogen required for the transformation.

$19\ C_6O_6H_{14}$ ’ $13\ C_6H_{14} + 36\ CO_2 + 42\ H_2O$

The above chemical reaction is exothermic and 1.5 mole of sorbitol generates 1 mole of hexane. When hydrogen is co-fed no carbon dioxide production takes place.

External links

- NIH Diabetes dictionary — see entry on sorbitol

References

1. ^ Production of Liquid Hydrocarbons from Biomass Jürgen O. Metzger Angewandte Chemie International Edition Volume 45, Issue 5 , Pages 696 - 698 *2005* Abstract

Potassium-sparing diuretics

Potassium-sparing diuretic refers to diuretic drugs that do not promote the secretion of potassium into the urine. They are used as adjunctive therapy, together with other drugs, in the treatment of hypertension and management of congestive heart failure.

Potassium-sparing diuretics do not share any obvious chemical similarities, except for the steroid-structure of the aldosterone antagonists. Those in clinical use include:

- Amiloride
- Triamterene
- Aldosterone antagonists
  - Spironolactone
  - Eplerenone

References

- Block JH, Beale JM. "Organic Medicinal and Pharmaceutical Chemistry" 11th edition. Lippincott Williams & Wilkins. 2004.

Thiazides

Thiazides are diuretics, a class of drug that promote water loss from the body. They inhibit Na+/Cl- reabsorption from the distal convoluted tubules in the kidneys. Thiazides also cause loss of potassium and an increase in serum uric acid. The chemical structure of the original thiazide diuretics contained a thiazide ring system; the term is also used for drugs with a similar action that are not chemically thiazides, such as chlortalidone and metolazone.

Thiazides are often used to treat hypertension. They are the recommended first-line treatment in the US (JNC VII) guidelines and a recommended treatment in the European (ESC/ESH) guidelines. They have been shown to prevent hypertension-related morbidity and mortality although the mechanism is not fully understood. They may cause vasodilation

by desensitizing the vascular smooth muscle cells to calcium release induced by norepinephrine (PMID 15611360).

Side effects can include hypokalemia, increased serum cholesterol, and impotence. The side effect of hypokalemia has motivated combining thiazides with ACE inhibitors, which also lower blood pressure but cause hyperkalemia as a side effect. Long-term usage of thiazides is also linked to increased levels of homocysteine, a toxic amino acid byproduct, has been associated with atherosclerosis. It is recommended that patients receiving long-term thiazide treaments also receive folic acid supplements to combat the risk.

Thiazides also lower urinary calcium excretion. That is why they are used to prevent calcium-containing kidney stones. This effect is associated with positive calcium balance and is associated with an increase in bone mineral density and reductions in fracture rates attributable to osteoporosis.

Thiazide treatment may be combined with ACE inhibitors to increase diuresis without changing plasma potassium concentrations. While ACE inhibitors cause diuresis with potassium retention, thiazide increases potassium excretion. Their combined effects on potassium cancel each other out.

It should be noted that thiazides pass through breast milk, and in some cases, decrease the flow of breast milk. There is no specific information regarding the use of thiazides in children, but it is still advised that mothers avoid using thiazides during the first month of breast feeding.

Mechanism of hypokalemia

Thiazide-induced hypokalemia (decreased plasma potassium concentration) is partly caused by the direct inhibition of the thiazide-sensitive NaCl transporter in the distal convoluted tubule, and also as a result of activation of the renin-angiotensin system. Decreased sodium reabsorption decreases the sodium gradient the nephron usually uses to reabsorb potassium, resulting in greater potassium excretion. In addition, the increased flow of tubular fluid increases the potassium gradient between the epithelium and lumen, driving the secretion of potassium. Finally, low blood volume induced by diuresis results in activation of the renin-angiotensin system, activating aldosterone, which significantly elevates the secretion of potassium. For this reason, ACE inhibitors, which inhibit angiotensin II production and therefore aldosterone activation, are frequently used in combination with thiazides to combat hypokalemia.

External links

- U.S. National Library of Medicine: Diuretics, Thiazide

Antimicrobials

An *antimicrobial* is a substance that kills or inhibits the growth of microbes such as bacteria (antibacterial activity), fungi (antifungal activity), viruses (antiviral activity), or parasites (anti-parasitic activity).

Main classes

Antibiotics

Antibiotics are generally used to treat bacterial infections. The toxicity to humans and other animals from antibiotics are generally considered to be low. However, prolonged use of certain antibiotics can decrease the number of gut flora, which can have a negative impact on health. Some recommend that during or after prolonged antibiotic use, that one should consume probiotics and eat reasonably to replace destroyed gut flora.

The term antibiotic originally described only those formulations derived from living organisms but is now applied also to synthetic antimicrobials, such as the sulfonamides.

The discovery, development, and clinical use of antibiotics during the 20th century have substantially decreased the morbidity and mortality from bacterial infections. The antibiotic era began with the therapeutic application of sulfonamide drugs in 1936, followed by a "golden" period of discovery from approximately 1945 to 1970, when a number of structurally diverse, highly effective agents were discovered and developed. However, since 1980 the introduction of new antimicrobial agents for clinical use has declined. Paralleled to this there has been an alarming increase in bacterial resistance to existing agents.[1] Antibiotics are among the most commonly used drugs. For example, 30% or more hospitalized patients are treated with one or more courses of antibiotic therapy. However, antibiotics are also among the drugs commonly misused by physicians, e.g. usage of antibiotic agents in viral respiratory tract infection. The inevitable consequence of widespread and injudicious use of antibiotics has been the emergence of antibiotic-resistant pathogens, resulting in the emergence of a serious threat to global public health. The resistance problem demands that a renewed effort be made to seek antibacterial agents effective against pathogenic bacteria resistant to current antibiotics. One of the possible strategies towards this objective is the rational localization of bioactive phytochemicals.

Traditional healers have long used plants to prevent or cure infectious disease. Many of these plants have been investigated scientifically for antimicrobial activity and a large number of plant products have been shown to inhibit the growth of pathogenic microorganisms. A number of these agents appear to have structures and modes of action that are distinct from those of the antibiotics in current use, suggesting that cross-resistance with agents already in use may be minimal. So, it is worthwhile to study plants and plant products for activity against resistant bacteria.

Essential oils

Many essential oils are included in pharmacopoeias as having antimicrobial activity, including:

- Oregano oil - in alternative medicine
Tea tree oil - in cosmetics, medicine
Mint oil - in medicine, cosmetics (tooth paste etc.)
Sandalwood oil - in cosmetics
Clove oil - stomatology etc.
Nigella sativa (Black cumin) oil
Onion oil (Allium cepe) - phytoncides, in phytotherapy
Leleshwa oil
Lavender oil
Lemon oil

- Eucalyptus **oil**

- Peppermint **oil**

- Cinnamon oil
Clove oil

Cations and elements

Many heavy metal cations such as Hg^{2+}, Cu^{2+}, and Pb^{2+} have antimicrobial activities, but are also very toxic to other living organisms, thus making them unsuitable for treating infectious diseases.

Ionic Silver is an excellent antimicrobial, with relatively low toxicity against non-target organisms. However, prolonged high intake of ionic silver may lead to health problems, such as argyria. In an inorganic matrix, silver ions are slowly released via an ion-exchange mechanism. The release of silver ions from the surface is slow, but just fast enough to maintain an effective concentration at and near the surface of the material. Once the silver ion leaves the surface of the matrix and reaches the surface of the microorganism, its mechanism of antimicrobial action begins. Uptake of silver ions by a microbial cell can occur by several mechanisms, including passive diffusion and active transport by systems that normally transport essential ions.

While the silver ions may bind non-specifically to cell surfaces and cause disruptions in cellular membrane function, it is widely believed that the antimicrobial properties of silver depend upon silver binding within the cell. Once inside the cell, silver ions begin to interrupt critical functions of the microorganism. Silver ions are highly reactive and readily bind to electron donor groups containing sulphur, oxygen and nitrogen, as well as negatively charged groups such as phosphates and chlorides. A prime molecular target for the silver ion resides in cellular thiol (-SH) groups, commonly found in critical proteins called enzymes. Enzymes become denatured because of conformational changes in the molecule that result

from silver ion binding. Many of the enzymes that silver ions denature are necessary in the cellular generation of energy.

If the energy source of the cell is incapacitated, the cell cannot maintain osmotic pressure, necessary substrates leak out of the cell and the microbe will quickly die. In addition to the well-known reaction of silver ions and proteins, several studies suggest that silver ions react with the base pairs of DNA, interfering with DNA replication. Studies on silver nanoparticles have shown antimicrobial activity, including activity against pathogenic Escherichia coli and HIV.

Reference

1. ^ Levy SB (ed) (1994) Drug Resistance: The New Apocalypse (special issue) Trends Microbiol 2: 341–425

Antibiotics

An *antibiotic* is a drug that kills or slows the growth of bacteria. They have no effect against viruses, fungi, or parasites. Antibiotics are one class of antimicrobials, a larger group which also includes anti-viral, anti-fungal, and anti-parasitic drugs. They are relatively harmless to the host, and therefore can be used to treat infections. The term, coined by Selman Waksman, originally described only those formulations derived from living organisms, in contrast to "chemotherapeutic agents", which are purely synthetic. Nowadays the term "antibiotic" is also applied to synthetic antimicrobials, such as the sulfa drugs. Antibiotics are generally small molecules with a molecular weight less than 2000. They are not enzymes. Some antibiotics have been derived from mold, for example the penicillin class.

Unlike previous treatments for infections, which included poisons such as strychnine and arsenic, antibiotics were labelled "magic bullets": drugs which targeted disease without harming the host. Conventional antibiotics are not effective in viral, fungal and other nonbacterial infections, and individual antibiotics vary widely in their effectiveness on various types of bacteria. Antibiotics can be categorised based on their target specificity: 'narrow-spectrum' antibiotics target particular types of bacteria, such as Gram-negative or Gram-positive bacteria, while 'wide-spectrum' antibiotics affect a larger range of bacteria.

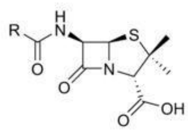
The effectiveness of individual antibiotics varies with the location of the infection, the ability of the antibiotic to reach the site of infection, and the ability of the bacteria to resist or inactivate the antibiotic. Some antibiotics actually kill the bacteria (bactericidal), whereas others merely prevent the bacteria from multiplying (bacteriostatic) so that the host's immune system can overcome them.

Oral antibiotics are the simplest approach when effective, with intravenous antibiotics reserved for more serious cases. Antibiotics may sometimes be administered topically, as with eyedrops or ointments.

Antibiotics can also be classified by the organisms against which they are effective, and by the type of infection in which they are useful, which depends on the sensitivities of the

organisms that most commonly cause the infection and the concentration of antibiotic obtainable in the affected tissue.

History


Penicillin

Many ancient cultures, including the ancient Egyptians, ancient Greeks and ancient Chinese, already used moulds and plants to treat infections. This worked because some moulds produce antibiotic substances. However, they couldn't distinguish or distil the active component in the moulds.

Modern research on antibiotics began in Britain with the discovery of Penicillin in 1928 by Alexander Fleming. More than ten years later, Ernst Chain and Howard Florey became interested in his work, and came up with the purified form of penicillin. The three shared the 1945 Nobel Prize in Medicine. "Antibiotic" was originally used to refer only to substances extracted from a fungus or other microorganism, but has come to include also the many synthetic and semi-synthetic drugs that have antibacterial effects.

Classes of antibiotics

At the highest level, antibiotics can be classified as either bactericidal or bacteriostatic. Bactericidals kill bacteria directly where bacteriostatics prevent them dividing. However, these classifications are based on laboratory behaviour; in practice, both of these will end a bacterial infection.

Antibiotics[1]

Class: **Aminoglycosides**

Infections caused by Gram-negative bacteria, such as Escherichia coli and Klebsiella. Side Effects: Hearing loss, Vertigo, Kidney damage

- Amikacin (Amikin)
- Gentamicin (Garamycin)
- Kanamycin
- Neomycin
- Netilmicin
- Streptomycin
- Tobramycin (Nebcin)

Class: Carbacephem

- Loracarbef (Lorabid)

Class: Carbapenems

- Ertapenem
- Imipenem/Cilastatin (Primaxin)
- Meropenem

Class: Cephalosporins (First generation)

Side Effects: Gastrointestinal upset and diarrhea. Nausea (if alcohol taken concurrently). Allergic reactions

- Cefadroxil (Duricef)
- Cefazolin (Ancef)
- Cephalexin (Keflex)

Class: Cephalosporins (Second generation)

Side Effects: Gastrointestinal upset and diarrhea. Nausea (if alcohol taken concurrently). Allergic reactions

- Cefaclor (Ceclor)
- Cefamandole (Mandole)
- Cefoxitin
- Cefprozil (Cefzil)
- Cefuroxime (Ceftin)

Class: Cephalosporins (Third generation)

Side Effects: Gastrointestinal upset and diarrhea. Nausea (if alcohol taken concurrently). Allergic reactions

- Cefixime
- Cefdinir (Omnicef)
- Cefditoren
- Cefoperazone (Cefobid)
- Cefotaxime (Claforan)
- Cefpodoxime
- Ceftazidime (Fortum)
- Ceftibuten
- Ceftizoxime
- Ceftriaxone (Rocephin)

Class: Cephalosporins (Fourth generation)

Side Effects: Gastrointestinal upset and diarrhea. Nausea (if alcohol taken concurrently). Allergic reactions

- Cefepime (Maxipime)

Class: **Glycopeptides**

- Teicoplanin
- Vancomycin (Vancocin)

Class: **Macrolides**

Streptococcal infections, syphilis, respiratory infections, mycoplasmal infections, Lyme disease. Side Effects: Nausea, vomiting, and diarrhea (especially at higher doses). Jaundice

- Azithromycin (Zithromax, Sumamed)
- Clarithromycin **(Biaxin)**
- Dirithromycin
- Erythromycin
- Roxithromycin
- Troleandomycin

Class: Monobactam

- Aztreonam

Class: **Penicillins**

Wide range of infections; penicillin used for streptococcal infections, syphilis, and Lyme disease. Side Effects: Gastrointestinal upset and diarrhea. Allergy with serious anaphylactic reactions. Brain and kidney damage (rare).

- Amoxicillin **(Novamox)**
- Ampicillin
- Azlocillin
- Carbenicillin
- Cloxacillin
- Dicloxacillin

    - Flucloxacillin
    - Mezlocillin
    - Nafcillin

- Penicillin

    - Piperacillin
    - Ticarcillin

Class: Polypeptides

Eye, ear or bladder infections; usually applied directly to the eye or inhaled into the lungs; rarely given by injection. Side Effects: Kidney and nerve damage (when given by injection).

- Bacitracin (Mupirocin)
- Colistin
- Polymyxin B

Class: **Quinolones**

Urinary tract infections, bacterial prostatitis, bacterial diarrhea, gonorrhea. Side Effects: Nausea (rare)

- Ciprofloxacin (Ciproxin, Ciplox)
- Enoxacin
- Gatifloxacin (Tequin)
- Levofloxacin (Levaquin)
- Lomefloxacin
- Moxifloxacin (Avelox)
- Norfloxacin
- Ofloxacin (Ocuflox)
- Trovafloxacin (Trovan)

Class: **Sulfonamides**

Urinary tract infections (except sulfacetamide and mafenide); mafenide is used topically for burns. Side Effects: Nausea, vomiting, and diarrhea. Allergy (including skin rashes). Crystals in urine. Kidney failure. Decrease in white blood cell count. Sensitivity to sunlight

- Mafenide
- Prontosil (archaic)
- Sulfacetamide
- Sulfamethizole
- Sulfanilimide (archaic)
- Sulfasalazine

- Sulfisoxazole
- Trimethoprim
- Trimethoprim-Sulfamethoxazole (Co-trimoxazole) (TMP-SMX) (Bactrim)

Class: **Tetracyclines**

Syphilis, chlamydial infections, Lyme disease, mycoplasmal infections, acne rickettsial infections. Side Effects: Gastrointestinal upset. Sensitivity to sunlight. Staining of teeth. Potential toxicity to mother and fetus during pregnancy

- Demeclocycline
- Doxycycline (Vibramycin)
- Minocycline
- Oxytetracycline

- Tetracycline **(Sumycin)**

Class: Others

- Chloramphenicol (Chloromycetin)
- Clindamycin (Cleocin)
- Ethambutol
- Fosfomycin
- Furazolidone
- Isoniazid
- Linezolid (Zyvox)
- Metronidazole (Flagyl)
- Nitrofurantoin (Macrodantin)
- Platensimycin
- Pyrazinamide
- Quinupristin/Dalfopristin (Syncercide)
- Rifampin
- Spectinomycin

Production

Since the first pioneering efforts of Florey and Chain in 1939, the importance of antibiotics to medicine has led to much research into discovering and producing them. The process of production usually involves screening of wide ranges of microorganisms, testing and modification. Production is carried out using fermentation; a process that is important in anaerobic conditions when there is no oxidative phosphorylation to maintain the production of ATP (Adenosine triphosphate) by glycolysis.

Side effects

Possible side effects are varied, and range from fever and nausea to major allergic reactions. One of the more common side effects is diarrhea, which results from the antibiotic disrupting the normal balance of intestinal flora, (which some people believe may be re-

balanced by taking probiotics). Other side effects can result from interaction with other drugs, such as elevated risk of tendon damage from administration of a quinolone antibiotic with a systemic corticosteroid.

It is a common assertion that some antibiotics can interfere with the efficiency of birth control pills. Although there remain few known cases of complication, the majority of antibiotics do not interfere with oral contraception, despite widespread misinformation to the contrary.[2]

Antibiotic misuse

Common forms of antibiotic misuse include failure to take the entire prescribed course of the antibiotic, usually because the patient feels better, but before the infecting organism is completely eradicated. In addition to treatment failure, these practices can result in antibiotic resistance in which the bacteria survive the abbreviated treatment. Taking antibiotics in inappropriate situations is another common form of antibiotic misuse. Common examples of this would be the use of antibacterials for viral infections such as the common cold.

In the United States, vast quantities of certain antibiotics are routinely included as low doses in the diet of some kinds of healthy farm animals, where this practice has been shown to make animals grow faster. Opponents of this practice, however, point out the likelihood that it also leads to an environment conducive to the evolution of antibiotic resistance, frequently in bacteria that are known to also infect humans. There has been no convincing evidence yet that the evolution of antibiotic resistance in such bacteria is actually occurring. As the majority of bacteria is killed in the pasteurization process applied to the milk, and the cooking of the meat, of such animals, any possible resistance may go unnoticed until the bacteria survives it. Theoretically, though, there is a significant possibility that such resistances could be transferred through bacterial plasmids, and the aforementioned conditions of continuous, low-dose antibiotics are ideal for the development of antibiotic resistance.

Excessive use of prophylactic antibiotics in travelers may also be classified as misuse.

Antibiotic resistance

Main article: Antibiotic resistance

Use or misuse of antibiotics may result in the development of antibiotic resistance by the infecting organisms, similar to the development of pesticide resistance in insects. Evolutionary theory of genetic selection requires that as close as possible to 100% of the infecting organisms be killed off to avoid selection of resistance; if a small subset of the population survives the treatment and is allowed to multiply, the average susceptibility of this new population to the compound will be much less than that of the original population, since they have descended from those few organisms which survived the original treatment. This survival often results from an inheritable resistance to the compound which was infrequent in the original population but is now much more frequent in the descendants thus selected entirely from those originally infrequent resistant organisms.

Antibiotic resistance has become a serious problem in both the developed and underdeveloped nations. By 1984 half of the people with active tuberculosis in the United States had a strain that resisted at least one antibiotic. In certain settings, such as hospitals and some child-care locations, the rate of antibiotic resistance is so high that the normal, low cost antibiotics are virtually useless for treatment of frequently seen infections. This leads to more frequent use of newer and more expensive compounds, which in turn leads inexorably to the rise of resistance to those drugs, and a never-ending ever-spiraling race to discover new and different antibiotics ensues, just to keep us from losing ground in the battle against infection. The fear is that we will eventually fail to keep up in this race, and the time when people did not fear life-threatening bacterial infections will be just a memory of a golden era.

Another example of selection is Staphylococcus aureus, which could be treated successfully with penicillin in the 1940s and 1950s. At present, nearly all strains are resistant to penicillin, and many are resistant to nafcillin, leaving only a narrow selection of drugs such as vancomycin useful for treatment. The situation is worsened by the fact that genes coding for antibiotic resistance can be transferred between bacteria, making it possible for bacteria never exposed to an antibiotic to acquire resistance from those which have. The problem of antibiotic resistance is worsened when antibiotics are used to treat disorders in which they have no efficacy, such as the common cold or other viral complaints, and when they are used widely as prophylaxis rather than treatment (as in, for example, animal feeds), because this exposes more bacteria to selection for resistance.

Beyond antibiotics

Unfortunately, the comparative ease of finding compounds which safely cured bacterial infections proved much harder to duplicate with respect to fungal and viral infections. Antibiotic research led to great strides in our knowledge of basic biochemistry and to the current biological revolution; but in the process it was discovered that the susceptibility of bacteria to many compounds which are safe to humans is based upon significant differences between the cellular and molecular physiology of the bacterial cell and that of the mammalian cell. In contrast, despite the seemingly huge differences between fungi and humans, the basic biochemistries of the fungal cell and the mammalian cell are much more similar; so much so that there are few therapeutic opportunities for compounds to attack a fungal cell which will not harm a human cell. Similarly, we know now that viruses represent an incredibly minimal intracellular parasite, being stripped down to a few genes worth of DNA or RNA and the minimal molecular equipment needed to enter a cell and actually take over the machinery of the cell to produce new viruses. Thus, the great bulk of viral metabolic biochemistry is not merely similar to human biochemistry, it actually is human biochemistry, and the possible targets of antiviral compounds are restricted to the relatively very few components of the actual virus itself.

Research into bacteriophages is ongoing at the moment. Bacteriophages are a specific type of virus that only targets bacteria. Research suggests that nature has evolved several types of bacteriophage for each type of bacteria. While research into bacteriophages is only in its infancy the results are promising and have already lead to major advances in microscopic imaging.[3] While bacteriophages provide a possible solution to the problem of

antibacterial resistance there is as of yet no proof that we will actually be able to deploy these microscopic killers in humans, we can only continue the research and see where it leads.

Phage therapy has been used in the past on humans in the US and Europe during the 1920s and 1930s, however due to not fully understanding the mechanism by which phage therapy worked, these treatments had mixed results. With the discovery of penicillin in the 1940s, Europe and the US changed to using antibiotics. However, in the former Soviet Union phage therapies continued to be studied. In the Republic of Georgia, the Eliava Institute of Bacteriophage, Microbiology & Virology continues to research the use of phage therapy. Various companies and foundations in North America and Europe are currently researching phage therapies.

References

1. ^ The Merck Manual of Medical Information - Home Edition, Robert Berkow (Ed.), Pocket (September, 1999), ISBN 0-671-02727-1.

2. ^ **Planned Parenthood:** Does taking antibiotics make the pill less effective?**, July 15, 2004**

3. ^ Purdue University "Biologists build better software, beat path to viral knowledge", see Imaging of Epsilon 15, a virus that infects the bacterium Salmonella News report

Aminoglycoside antibiotics

Aminoglycosides are a group of antibiotics that are effective against certain types of bacteria. They include amikacin, gentamicin, kanamycin, neomycin, netilmicin, paromomycin, streptomycin, tobramycin and apramycin. Those which are derived from Streptomyces genus are named with the suffix -mycin, while those which are derived from micromonospora are named with the suffix -micin.

Mechanism of action

Aminoglycosides work by binding to the bacterial 30S ribosomal subunit (some work by binding to the 50s subunit), inhibiting the translocation of the peptidyl-tRNA from the A-site to the P-site and also causing misreading of mRNA, leaving the bacterium unable to synthesize proteins vital to its growth. But their exact mechanism of action is not fully known.

Spectrum of activity

Aminoglycosides are useful primarily in infections involving aerobic, Gram-negative bacteria, such as Pseudomonas, Acinetobacter, and Enterobacter. In addition, some mycobacteria, including the bacteria that cause tuberculosis, are susceptible to

aminoglycosides. The most frequent use of aminoglycosides is empiric therapy for serious infections such as septicemia, complicated intraabdominal infections, complicated urinary tract infections, and nosocomial respiratory tract infections. Usually, once cultures of the causal organism are grown and their susceptibilities tested, aminoglycosides are discontinued in favor of less toxic antibiotics.

Streptomycin was the first effective drug in the treatment of tuberculosis, though the role of aminoglycosides such as streptomycin and amikacin has been eclipsed (because of their toxicity and inconvenient route of administration) except for multiple drug resistant strains.

Infections caused by Gram-positive bacteria can also be treated with aminoglycosides, but other types of antibiotics are more potent and less damaging to the host. In the past the aminoglycosides have been used in conjunction with beta-lactam antibiotics in streptococcal infections for their synergistic effects, particularly in endocarditis. One of the most frequent combinations is Ampicillin (a beta-lactam, or penicillin-related antibiotic) and Gentamicin. Often, hospital staff refer to this combination as "amp and gent" or more recently called "pen and gent" for penicillin and gentamycin.

Aminoglycosides are mostly ineffective against anaerobic bacteria, fungi and viruses.

Toxicity

Because of their potential for ototoxicity and nephrotoxicity (kidney toxicity), aminoglycosides are administered in doses based on body weight. Blood drug levels and creatinine are monitored during the course of therapy. Serum creatinine measurements are used to estimate how well the kidneys are functioning and as a marker for kidney damage caused by these drugs.

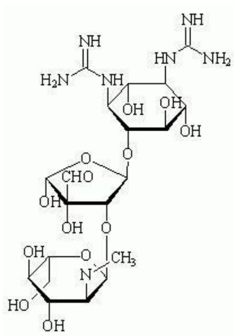
Routes of administration

Since they are not absorbed from the gut, they are administered intravenously and intramuscularly. Some are used in topical preparations for wounds. Oral administration can be used for gut decontamination (e.g. in hepatic encephalopathy).

Specific Agents

- Amikacin (Amikin®) - Gentamicin (Garamycin®) - Kanamycin (Kantrex®) - Neomycin - Netilmicin (Netromycin®) - Streptomycin - Tobramycin (Nebcin®)

Streptomycin



Systematic (IUPAC) name

5-(2,4-diguanidino-3,5,6-trihydroxy-cyclohexoxy)-4- [4,5-dihydroxy-6-(hydroxymethyl)

-3-methylamino-tetrahydropyran-2-yl] oxy-3-hydroxy-2-methyl-tetrahydrofuran-3-carbaldehyde

Identifiers

CAS number 57-92-1

ATC code A07**AA04** J01**GA01**

PubChem 19649

DrugBank APRD00412

Chemical data

Formula $C_{21}H_{39}N_7O_{12}$

Mol. weight 581.574 g/mol

Physical data

Melt. point 12 °C (54 °F)

Streptomycin is an antibiotic drug, the first of a class of drugs called aminoglycosides to be discovered, and was the first antibiotic remedy for tuberculosis. It is derived from the actinobacterium Streptomyces griseus. Streptomycin stops bacterial growth by damaging cell membranes and inhibiting protein synthesis. Specifically, it binds to the 16S rRNA of the bacterial ribosome, which prevents the release of the growing protein (polypeptide chain). Humans have structurally different ribosomes than bacteria, thereby allowing the selectivity of this antibiotic for bacteria. Streptomycin cannot be given orally, but must be administered

by regular intramuscular injection. An adverse effect of this medicine is ototoxicity. It can result in permanent hearing loss.

History

It was first isolated on October 19, 1943 in the laboratory of Selman Abraham Waksman at Rutgers University by Albert Schatz, a graduate student in his laboratory. Waksman and his laboratory discovered several antibiotics, including actinomycin, clavacin, streptothricin, streptomycin, grisein, neomycin, fradicin, candicidin, candidin, and others. Two of these, streptomycin and neomycin, found extensive application in the treatment of numerous infectious diseases. Streptomycin was the first antibiotic that could be used to cure the disease tuberculosis. Waksman is credited with having coined the term antibiotics.

The details and credit for the discovery of streptomycin were strongly contested by Albert Schatz and resulted in litigation. The contention arose because Schatz was the graduate student in charge of performing the lab work on streptomycin; however, it was argued that he was using techniques, equipment and lab space of Waksman's while under Waksman's direction. There is contention as to whether or not Schatz should have been included in the Nobel Prize awarded in 1952. However, the committee stated that the Nobel Prize was awarded not only for the discovery of streptomycin but also for the development of the methods and techniques that led up to its discovery and the discovery of many other antibiotics.

The litigation ended with a settlement for Schatz and the official decision that Waksman and Schatz would be considered co-discoverers of streptomycin. Schatz was awarded the Rutgers medal in 1994, at the age of 74. The controversy ultimately had a negative impact on the careers of both Waksman and Schatz and the controversy continues today.

Uses

- Tuberculosis in combination with other anti-TB drugs
- Yersinia pestis known popularly by one of its varients, the Bubonic Plague has been treated using this, Chloramphenicol, and Tetracycline.

Beta-lactam antibiotics

^{2}-lactam antibiotics are a broad class of antibiotics which include penicillin derivatives, cephalosporins, monobactams, carbapenems and ^{2}-lactamase inhibitors; basically any antibiotic agent which contains a ^{2}-lactam nucleus in its molecular structure. They are the most widely used group of antibiotics available.

Clinical use

^{2}-lactam antibiotics are indicated for the prophylaxis and treatment of bacterial infections caused by susceptible organisms. Whilst traditionally ^{2}-lactam antibiotics were

mainly active only against Gram-positive bacteria, the development of broad-spectrum ²-lactam antibiotics active against various Gram-negative organisms has increased their usefulness.

Mode of action

²-Lactam antibiotics are bactericidal, and act by inhibiting the synthesis of the peptidoglycan layer of bacterial cell walls. The peptidoglycan layer is important for cell wall structural integrity, especially in Gram-positive organisms. The final transpeptidation step in the synthesis of the peptidoglycan is facilitated by transpeptidases known as penicillin binding proteins (PBPs).

²-lactam antibiotics are analogues of D-alanyl-D-alanine - the terminal amino acid residues on the precursor NAM/NAG-peptide subunits of the nascent peptidoglycan layer. The structural similarity between ²-lactam antibiotics and D-alanyl-D-alanine facilitates their binding to the active site of penicillin binding proteins (PBPs). The ²-lactam nucleus of the molecule irreversibly binds to (acylates) the Ser***403*** residue of the PBP active site. This irreversible inhibition of the PBPs prevents the final crosslinking (transpeptidation) of the nascent peptidoglycan layer, disrupting cell wall synthesis. Inhibition of PBPs may also lead to the activation of autolytic enzymes in the bacterial cell wall.

Modes of resistance

By *definition*, all ²-lactam antibiotics have a ²-lactam ring in their structure. The effectiveness of these antibiotics relies on their ability to reach the PBP intact and their ability to bind to the PBP. Hence, there are 2 main modes of bacterial resistance to ²-lactams, as discussed below.

The first mode of ²-lactam resistance is due to enzymatic hydrolysis of the ²-lactam ring. If the bacteria produces the enzymes ²-lactamase or penicillinase, these enzymes will break open the ²-lactam ring of the antibiotic, rendering the antibiotic ineffective. The genes encoding these enzymes may be inherently present on the bacterial chromosome or may be acquired via plasmid transfer, and beta-lactamase gene expression may be induced by exposure to beta-lactams. The production of a ²-lactamase by a bacterium does not necessarily rule out all treatment options with ²-lactam antibiotics. In some instances, ²-lactam antibiotics may be co-administered with a ²-lactamase inhibitor.

However, in all cases where infection with ²-lactamase-producing bacteria is suspected, the choice of a suitable ²-lactam antibiotic should be carefully considered prior to treatment. In particular, choosing appropriate ²-lactam antibiotic therapy is highly important against organisms with inducible ²-lactamase expression. If ²-lactamase production is inducible, then failure to use the most appropriate ²-lactam antibiotic therapy at the onset of treatment will result in induction of ²-lactamase production, thereby making further efforts with other ²-lactam antibiotics more difficult.

The second mode of ²-lactam resistance is due to possession of altered penicillin binding proteins. ²-lactams cannot bind as effectively to these altered PBPs, and as a result, the ²-lactams are less effective at disrupting cell wall synthesis. Notable examples of this mode of resistance include methicillin-resistant Staphylococcus aureus (MRSA) and penicillin-

resistant Streptococcus pneumoniae. Altered PBPs do not necessarily rule out all treatment options with ²-lactam antibiotics.

Common 2-lactam antibiotics

Penicillins

Main article: penicillin

Narrow spectrum penicillins

- benzathine penicillin
- benzylpenicillin **(penicillin G)**
- phenoxymethylpenicillin **(penicillin V)**
- procaine penicillin

Narrow spectrum penicillinase-resistant penicillins

- methicillin
dicloxacillin
flucloxacillin

Moderate spectrum penicillins

- amoxicillin
- ampicillin

Broad spectrum penicillins

- co-amoxiclav (amoxycillin+clavulanic acid)

Extended Spectrum Penicillins

- azlocillin
carbenicillin
ticarcillin

mezlocillin
piperacillin

Cephalosporins

Main article: cephalosporin

First generation cephalosporins

Moderate spectrum.

- cefalexin
- cephalothin
- cefazolin

Second generation cephalosporins

Moderate spectrum with anti-Haemophilus activity.

- cefaclor
- cefuroxime
- cefamandole

Second generation cephamycins

Moderate spectrum with anti-anaerobic activity.

- cefotetan
- cefoxitin

Third generation cephalosporins

Broad spectrum.

- ceftriaxone
- cefotaxime

Broad spectrum with anti-Pseudomonas activity.

- ceftazidime

Fourth generation cephalosporins

Broad spectrum with enhanced activity against Gram positive bacteria and beta-lactamase stability.

- cefepime
- cefpirome

Carbapenems

Main article: carbapenem

Broadest spectrum of beta-lactam antibiotics.

- imipenem (with cilastatin)
- meropenem
- ertapenem
- faropenem

Monobactams

Unlike other beta-lactams, there is no fused ring attached to beta-lactam nucleus. Thus, there is less probability of cross-sensitivity reactions.

- aztreonam (Azactam®)

Beta-lactamase inhibitors

No antimicrobial activity. Their sole purpose is to prevent the inactivation of beta-lactam antibiotics by beta-lactamases, and as such, they are co-administered with beta-lactam antibiotics.

- clavulanic acid
- tazobactam
- sulbactam

Adverse effects

Adverse drug reactions

Common adverse drug reactions (ADRs) for the ^{2}-lactam antibiotics include: diarrhea, nausea, rash, urticaria, superinfection (including candidiasis). (Rossi, 2004)

Infrequent ADRs include: fever, vomiting, erythema, dermatitis, angioedema, pseudomembranous colitis. (Rossi, 2004)

Pain and inflammation at the injection site is also common for parenterally-administered ^{2}-lactam antibiotics.

Allergy/hypersensitivity

Allergic reactions to any ^{2}-lactam antibiotic may occur in up to 10% of patients receiving that agent. Anaphylaxis will occur in approximately 0.01% of patients. (Rossi, 2004) There is perhaps a 5-10% cross-sensitivity between penicillin-derivatives, cephalosporins and carbapenems; but this figure has been challenged by various investigators.

Nevertheless, the risk of cross-reactivity is sufficient to warrant the contraindication of all ²-lactam antibiotics in patients with a history of severe allergic reactions (urticaria, anaphylaxis, interstitial nephritis) to any ²-lactam antibiotic.

References

- Rossi S (Ed.) (2004). Australian Medicines Handbook 2004. Adelaide: Australian Medicines Handbook. ISBN 0-9578521-4-2.

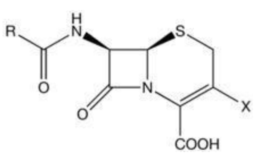
Carbapenem antibiotics

Carbapenems are a class of **beta-lactam antibiotics**.

The following drugs belong to the carbapenem class:

- Imipenem (often given as part of Imipenem/cilastatin) Meropenem
Ertapenem
Faropenem
Doripenem
Panipenem/betamipron

Cephalosporin antibiotics



Cephalosporin nucleus

The *cephalosporins* (IPA: [Ìk[fYloÈspTrYn, Ìs[fY-]) are a class of ²-lactam antibiotics. Together with cephamycins they belong to a sub-group called cephems.

History

Cephalosporin compounds were first isolated from cultures of Cephalosporium acremonium from a sewer in Sardinia in 1948 by Italian scientist Giuseppe Brotzu. He noticed that these cultures produced substances that were effective against Salmonella typhi, the cause of typhoid fever. Researchers at the Sir William Dunn School of Pathology at the University of Oxford isolated cephalosporin C, which had stability to ²-lactamases but was not sufficiently potent for clinical use. The cephalosporin nucleus, 7-aminocephalosporanic acid (7-ACA), was derived from cephalosporin C and proved to be analogous to the penicillin nucleus 6-aminopenicillanic acid. Modification of the 7-ACA side-chains resulted in the development of useful antibiotic agents, and the first agent cephalothin (cefalotin) was launched by Eli Lilly in 1964.

Mode of action

Cephalosporins are bactericidal and have the same mode of action as other beta-lactam antibiotics (such as penicillins). Cephalosporins disrupt the synthesis of the peptidoglycan layer of bacterial cell walls. The peptidoglycan layer is important for cell wall structural integrity, especially in Gram-positive organisms. The final transpeptidation step in the synthesis of the peptidoglycan is facilitated by transpeptidases known as penicillin binding proteins (PBPs).

Clinical use

Indications

Cephalosporins are indicated for the prophylaxis and treatment of bacterial infections caused by susceptible organisms. First-generation cephalosporins are predominantly active against Gram-positive bacteria, and successive generations have increased activity against Gram-negative bacteria (albeit often with reduced activity against Gram-positive organisms).

Adverse effects

Common adverse drug reactions (ADRs) (e1% of patients) associated with cephalosporin therapy include: diarrhea, nausea, rash, electrolyte disturbances, and/or pain and inflammation at injection site. Infrequent ADRs (0.1–1% of patients) include: vomiting, headache, dizziness, oral and vaginal candidiasis, pseudomembranous colitis, superinfection, eosinophilia, and/or fever.

Approximately 5–10% of patients with allergic hypersensitivity to penicillins and/or carbapenems will also have cross-reactivity with cephalosporins. Thus, they are contraindicated in patients with a history of severe of immediate allergic reactions (urticaria, anaphylaxis, interstitial nephritis, etc) to penicillins, carbapenems or cephalosporins.[1]

Classification

The cephalosporin nucleus can be modified to gain different properties. Cephalosporins are sometimes grouped into "generations" by their antimicrobial properties. The first cephalosporins were designated first generation while later, more extended spectrum cephalosporins were classified as second generation cephalosporins. Each newer generation of cephalosporins has significantly greater Gram-negative antimicrobial properties than the preceding generation, in most cases with decreased activity against Gram-positive organisms. Fourth generation cephalosporins, however, have true broad spectrum activity.

The classification of cephalosporins into "generations" is commonly practised, although the exact categorisation of cephalosporins is often imprecise. For example, the fourth generation of cephalosporins is not yet recognized in Japan. In Japan, cefaclor is classed as a first generation cephalosporin; and cefbuperazone, cefminox and cefotetan are classed as second generation cephalosporins. Cefbuperazone, cefminox, and cefotetan are classed as

second generation cephems. Cefmetazole and cefoxitin are classed as third generation cephems. Flomoxef, latamoxef are in a new class called oxacephems.

Most first generation cephalosporins were originally spelt "ceph-" in English-speaking countries. This continues to be the preferred spelling in North America and Australia, while European countries have adopted International Nonproprietary Names, which are usually spelt "cef-". Newer first-generation cephalosporins and all cephalosporins of later generations are spelt "cef-".

First generation

First generation cephalosporins are moderate spectrum agents, with a spectrum of activity that includes penicillinase-producing, methicillin-susceptible staphylococci and streptococci, though they are not the drugs of choice for such infections. They also have activity against some Escherichia coli, Klebsiella pneumoniae and Proteus mirabilis, but have no activity against Bacteroides fragilis, enterococci, methicilllin-resistant staphylococci, Pseudomonas, Acinetobacter, Enterobacter, indole-positive Proteus or Serratia.

- Cefacetrile (cephacetrile)

Cefadroxil (cefadroxyl; Duricef®)
Cefalexin (cephalexin; Keflex®)
Cephaloglycin
Cefalonium (cephalonium)
Cefaloridine (cephaloradine)
Cefalotin (cephalothin; Keflin®)
Cefapirin (cephapirin; Cefadryl®)
Cefatrizine
Cefazaflur
Cefazedone
Cefazolin (cephazolin; Ancef®, Kefzol®)
Cefradine (cephradine; Velosef®)
Cefroxadine
Ceftezole

Second generation

The second generation cephalosporins have a greater Gram-negative spectrum while retaining some activity against Gram-positive cocci. They are also more resistant to beta-lactamase.

- Cefaclor (Ceclor®)

Cefonicid (Monocid®)
Cefprozil (cefproxil; Cefzil®)
Cefuroxime (Zinnat®, Zinacef®, Ceftin®)
Cefuzonam

Second generation cephalosporins with antianaerobe activity

- Cefamandole
Ceforanide
Cefotiam

The following cephems are also sometimes grouped with second-generation cephalosporins:

- Carbacephems: loracarbef (Lorabid®)
Cephamycins: cefbuperazone, cefmetazole (Zefazone®), cefminox, cefotetan (Cefotan®), cefoxitin (Mefoxin®)

Third generation

Third generation cephalosporins have a broad spectrum of activity and further increased activity against Gram-negative organisms. Some members of this group (particularly those available in an oral formulation, and those with anti-pseudomonal activity) have decreased activity against Gram-positive organisms. They may be particularly useful in treating hospital-acquired infections, although increasing levels of extended-spectrum beta-lactamases are reducing the clinical utility of this class of antibiotics.

- Cefcapene
Cefdaloxime
Cefdinir (Omnicef®)
Cefditoren
Cefetamet
Cefixime (Suprax®)
Cefmenoxime
Cefodizime
Cefoperazone (Cefobid®)
Cefotaxime (Claforan®)
Cefpimizole
Cefpodoxime (Vantin®)
Cefteram
Ceftibuten (Cedax®)
Ceftiofur
Ceftiolene
Ceftizoxime (Cefizax®)
Ceftriaxone (Rocephin®)

Third generation cephalosporins with antipseudomonal activity

- Ceftazidime (Fortum®, Fortaz®)
Cefpiramide
Cefsulodin

The following cephems are also sometimes grouped with third-generation cephalosporins:

- Oxacephems: latamoxef (moxalactam)

Fourth generation

Fourth generation cephalosporins are extended-spectrum agents with similar activity against Gram-positive organisms as first-generation cephalosporins. They also have a greater resistance to beta-lactamases than the third generation cephalosporins. Many can cross blood brain barrier and are effective in meningitis.

- Cefclidine
Cefepime (Maxipime®)
Cefluprenam
Cefoselis
Cefozopran
Cefpirome
Cefquinome

The following cephems are also sometimes grouped with third-generation cephalosporins:

- Oxacephems: flomoxef

Yet to be classified

These cephems have progressed far enough to be named, but have not been assigned to a particular generation. Ceftobiprole (and the oral medocaril version) are on the FDA fast track. Ceftobiprole has powerful antipseudomonal characteristics and appears to be less susceptible to development of resistance.

- Cefaclomezine
Cefaloram
Cefaparole
Cefcanel
Cefedrolor
Cefempidone
Cefetrizole
Cefivitril
Cefmatilen
Cefmepidium
Cefovecin
Cefoxazole
Cefrotil
Cefsumide
Ceftioxide
Ceftobiprole (previously BAL 9141 and RO 63-9141)
Ceftobiprole (previously BAL 5788)
Cefuracetime

References

1. ^ Rossi S, editor. Australian Medicines Handbook 2006. Adelaide: Australian Medicines Handbook; 2006.

See also

- Beta-lactam antibiotic

AGG01

AGG01 is the tentative name of a new Penicillin-class antibiotic, recently as of October 2006 discovered in the breast milk of the Tammar Wallaby, reportedly one hundred times more powerful than penicillin.

This compound was found to be effective against MRSA, E. coli, Streptococci, Salmonella, Bacillus subtilus, Pseudomonas spp, Proteus vulgaris, and Staphylococcus aureus.

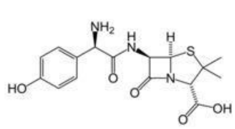
AGG01 has not yet been classified as a Beta-lactam antibiotic.

AGG01 is a cationic peptide, which is a polycationic protein which is rich in positive residues of the amino acidss arginine and lysine, and which folds into an amphipathic structure (one which has both hydrophobic and hydrophilic areas). These features mean that it can interact with the anionic lipids in the bacterial membrane, such as phosphatidylglycerol. It inserts itself into the membrane, by competing with cross-linking proteins between each membrane layer, and then sets up trans-membrane protein channels which induce ion transport out of the cell. This causes huge leakage via osmosis through these 'pores' and the general consensus is that the loss of these essential molecules is the mechanism by which bacteria are killed. The bacterial membrane has a different structure from the mammalian plasma membrane, so the protein can only kill pathogenic cells and not human ones.[1]

References

1. ^ Fighting superbugs with milk. NewScientist.com (2006-04-20). Retrieved on 2006-09-07.

Amoxicillin



***Amoxicillin* Systematic (IUPAC) name**

7-[2-amino-2-(4-hydroxyphenyl) -acetyl]amino-3,3-dimethyl-6-oxo -2-thia-5-azabicyclo[3.2.0]heptane -4-carboxylic acid

Identifiers

CAS number 26787-78-0

ATC code **J01**CA04

PubChem 33613

DrugBank APRD00248

Chemical data

Formula $C_{16}H_{19}N_{3}O_{5}S$

Mol. weight 365.4 g/mol

Pharmacokinetic data

Bioavailability 95% oral

Metabolism less than 30% Hepatic biotransformed

Half life 61.3 minutes

Excretion renal

Therapeutic considerations

Pregnancy cat. A$_{(AU)}$

Legal status POM$_{(UK)}$

Routes oral, intravenous

Amoxicillin (INN) or *amoxycillin* (former BAN) is a moderate-spectrum ^{2}-lactam antibiotic used to treat bacterial infections caused by susceptible microorganisms. It is usually the drug of choice within the class because it is better absorbed, following oral administration, than other beta-lactam antibiotics. Amoxicillin is susceptible to degradation by ^{2}-lactamase-producing bacteria, and so may be given with clavulanic acid to decrease its susceptibility (see below). It is currently marketed by GlaxoSmithKline under the trade name *Amoxil*.

Mode of action

Amoxicillin acts by inhibiting the synthesis of bacterial cell walls. It inhibits cross-linkage between the linear peptidoglycan polymer chains that make up a major component of the cell wall of Gram-positive bacteria.

Main article: beta-lactam antibiotic

Microbiology

Amoxicillin is a moderate-spectrum antibiotic active against a wide range of Gram-positive, and a limited range of Gram-negative organisms. Some examples of susceptible and resistant organisms, from the Amoxil® Approved Product Information (GSK, 2003), are listed below.

Susceptible Gram-positive organisms

Streptococcus spp., Diplococcus pneumoniae, non ²-lactamase-producing Staphylococcus spp., and Streptococcus faecalis.

Susceptible Gram-negative organisms

Haemophilus influenzae, Neisseria gonorrhoeae, Neisseria meningitidis, Escherichia coli, Proteus mirabilis and Salmonella spp.

Resistant organisms

Penicillinase-producing organisms, particularly penicillinase-producing Staphylococcus spp. Penicillinase-producing N. gonorrhoeae and H. influenzae are also resistant.

All strains of Pseudomonas spp., Klebsiella spp., Enterobacter spp., indole-positive Proteus spp., Serratia marcescens, and Citrobacter spp. are resistant.

The incidence of ²-lactamase-producing resistant organisms, including E. coli, appears to be increasing.

Doubling the routinely given concentration (in pediatrics) of amoxicillin has been shown to eradicate intermediately resistant organisms (Red Book, 2003 Report of the Committee on Infectious Diseases, American Academy of Pediatrics).

Formulations

Amoxicillin in trihydrate form is available as capsules, tablets, or syrup for oral use, and as the sodium salt for intravenous administration. It is one of the most common antibiotics issued to children.

Amoxicillin and clavulanic acid

Main article: Co-amoxiclav

Amoxicillin (in either trihydrate or sodium salt forms) may be combined with Clavulanic acid (as potassium clavulanate), a ²-lactamase inhibitor, to increase the spectrum of action against Gram-negative organisms, and to overcome bacterial antibiotic resistance mediated through ²-lactamase production. This formulation is referred to as Co-amoxiclav (British Approved Name), but commonly by proprietary names such as Augmentin and Clamoxyl.

Side Effects

Side effects are as those for Beta-lactam antibiotic Adverse effects.

Proprietary preparations

The patent for amoxicillin has expired. Thus amoxicillin is marketed under many trade names including: Actimoxi®, Amoksiklav®, Amoxibiotic®, Amoxicilina®, Apo-Amoxi®, Cilamox®, Dispermox®, Isimoxin®, Lamoxy®, Ospamox®, Pamoxicillin®, Polymox®, Sinacilin®, Trimox®, Tolodina®, Wymox®, Zerrsox® and Zimox®.

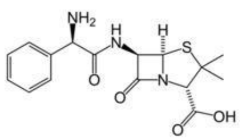
Trivia

Amoxicillin is often known for its unappealing taste and odor.

References

- Neal, MJ (2002). Medical Pharmacology at a Glance (4 ed.). Oxford: Blackwell Science. ISBN 0-632-05244-9
- British National Formulary 45 March 2003

Ampicillin



Systematic (IUPAC) name 7-(2-amino-2-phenyl-acetyl)amino-3,3 -dimethyl-6-oxo-2-thia-5-azabicyclo [3.2.0]heptane-4-carboxylic acid

Identifiers

CAS number 69-53-4

ATC code **J01**CA01

PubChem 149171

DrugBank APRD00320

Chemical data

Formula C16H18N3O4S

Mol. weight 349.406 g/mol

Pharmacokinetic data

Bioavailability 40% (oral)

Protein binding 15 to 25%

Half life approx 1 hour

Excretion 75 to 85% renal

Therapeutic considerations

Pregnancy cat. A (Au), B (U.S.)

Routes Oral, intravenous

Ampicillin is a beta-lactam antibiotic that has been used extensively to treat bacterial infections since 1961. It can sometimes result in allergic reactions that range in severity from a rash (i.e. patients with mononucleosis) to potentially lethal anaphylaxis.

Mechanism of action

Belonging to the group of beta-lactam antibiotics, ampicillin is able to penetrate Gram-positive and some Gram-negative bacteria. It inhibits the third and final stage of bacterial cell wall synthesis, which ultimately leads to cell lysis.

Indications

Ampicillin is closely related to amoxicillin, another type of penicillin, and both are used to treat urinary tract infections, otitis media, uncomplicated community-acquired pneumonia, Haemophilus influenzae, salmonellosis and Listeria meningitis. It is used with flucloxacillin in the combination antibiotic co-fluampicil for empiric treatment of cellulitis; providing cover against Group A streptococcal infection whilst the flucloxacillin acts against the Staphylococcus aureus bacterium. Of concern is the number of bacteria that become resistant to Ampicillin necessitating combination therapy or use of other antibiotics.

Use in research

Ampicillin is often used in molecular biology as a test for the uptake of genes (e.g., by plasmids) by bacteria (e.g., E. coli). A gene that is to be inserted into a bacterium is coupled to a gene coding for an ampicillin resistance (in E. coli, usually the bla gene, coding for ²-lactamase). The treated bacteria are then grown on a medium containing ampicillin. Only the bacteria that successfully take up the desired genes become ampicillin resistant, and therefore contain the other desired gene as well.

Co-amoxiclav

Co-amoxiclav is the British Approved Name, in the British Pharmacopoeia, for the combination antibiotic containing Amoxicillin (as either trihydate or the sodium salt) and Clavulanic acid (as Potassium clavulanate). This name, unlike co-trimoxazole, has not been widely adopted internationally and the combination product is usually referred to by various names such as *amoxicillin with clavulanic acid* or *amoxicillin+clavulanate* or simply by the trade name. Co-amoxiclav is currently marketed under various trade names including *Augmentin* (GlaxoSmithKline), and for veterinary use as *Clavamox* (Pfizer) and *Clavaseptin* (Vétoquinol).

The combination of amoxicillin, a ^{2}-lactam antibiotic; with clavulanic acid, a ^{2}-lactamase inhibitor; results in an antibiotic with an increased spectrum of action and restored efficacy against ^{2}-lactamase producing amoxicillin-resistant bacteria.

Dosage

The proportions of the two constituents are expressed as x/y where x and y are the strengths in milligrams of amoxicillin and clavulanic acid respectively. However, the branded products indicate their strengths as the total combined antibiotic quantity, hence co-amoxiclav 250/125 a Augmentin 375 and contains 250 mg of amoxicillin with 125 mg of clavulanic acid.

Standard adult dosages for respiratory tract, urinary, abdominal and dental infections as well as cellulitis and animal bites is co-amoxiclav 250/125 (one tablet Augmentin 375) taken every 8 hours, which may be doubled in severe infections (either as two tablets at a time of Augmentin 375, or a single tablet of co-amoxiclav 500/125 a Augmentin 625). In the US, Augmentin XR (co-amoxiclav 1000/62.5) is marketed for use in community acquired pneumonia with two tablets taken twice a day (giving 4000 mg total daily dose of amoxicillin).

Dosages for children are also given three times a day using suspensions containing co-amoxiclav 250/62 in each 5 mL (Augmentin '250/62 SF') for those between the ages of 6 - 12 years and co-amoxiclav 125/31 (Augmentin '125/31 SF') for those between the ages of 1 - 6 years. A more concentrated solution, co-amoxiclav 400/57 (Augmentin Duo), may be administered more conveniently just twice daily to children from as young as 2 months of age; quantities are based on body weight with 2.5 mL from the age of 2 years and 5 mL after the age of 6 years.

Side effects

Amongst the possible side-effects of this medication are diarrhoea, vomiting and a few other conditions. These do not usually require medical attention. However, if the patient experiences an allergic reaction to the medication, jaundice, fever or severe diarrhoea, it is necessary to contact a doctor immediately. As with all antimicrobial agents, pseudomembranous colitis has been associated with the use of amoxicillin-clavulanate.

Amoxicillin is a member of the penicillin family of antibiotics, and therefore should not be taken by patients allergic to penicillin.

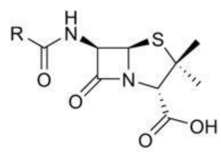
Veterinary use

The amoxicillin/clavulanic acid combination is also used in the treatment of, amongst other infections, periodontitis in dogs and skin infections in cats. The preparation for veterinary use is commonly marketed under the trade names *Clavaseptin*, and *Clavamox*.

References

- British National Formulary 45 March 2003

Penicillin



Penicillin nucleus

Penicillin (sometimes abbreviated *PCN*) refers to a group of ²-lactam antibiotics used in the treatment of bacterial infections caused by susceptible, usually Gram-positive, organisms. The name “penicillin” can also be used in reference to a specific member of the penicillin group. All penicillins possess the basic Penam Skeleton, which has the molecular formula R-C9H11N2O4S, where R is a variable side chain.

History

The discovery of penicillin is usually attributed to Scottish scientist Alexander Fleming in 1928, though others had earlier noted the antibacterial effects of Penicillium. Fleming, at his laboratory in St. Mary's Hospital (Now one of Imperial College teaching hospitals) in London, noticed a halo of inhibition of bacterial growth around a contaminant blue-green mould on a Staphylococcus plate culture. Fleming concluded that the mould was releasing a substance that was inhibiting bacterial growth and lysing the bacteria. He grew a pure culture of the mould and discovered that it was a Penicillium mould, now known to be Penicillium chrysogenum. Fleming coined the term "penicillin" to describe the filtrate of a broth culture of the Penicillium mould. Even in these early stages, penicillin was found to be most effective against Gram-positive bacteria, and ineffective against Gram-negative organisms and fungi. He expressed initial optimism that penicillin would be a useful disinfectant, being highly potent with minimal toxicity compared to antiseptics of the day, but particularly noted its laboratory value in the isolation of "Bacillus influenzae" (now Haemophilus influenzae).[1] After further experiments, Fleming was convinced that penicillin could not last long enough in the human body to kill pathogenic bacteria and stopped studying penicillin after 1931, but

restarted some clinical trials in 1934 and continued to try to get someone to purify it until 1940.

In 1939, Australian scientist Howard Walter Florey and a team of researchers (Ernst Boris Chain, A. D. Gardner, Norman Heatley, M. Jennings, J. Orr-Ewing and G. Sanders) at the Sir William Dunn School of Pathology, University of Oxford made significant progress in showing the in vivo bactericidal action of penicillin. Their attempts to treat humans failed due to insufficient volumes of penicillin, but they proved its harmlessness and effect in mice. Some of the pioneering trials of penicillin took place at the Radcliffe Infirmary in Oxford. On 1942-03-14 John Bumstead and Orvan Hess became the first in the world to successfully treat a patient using penicillin.[2][3]

During World War II, penicillin made a major difference in the number of deaths and amputations caused by infected wounds amongst Allied forces. Availability was severely limited, however, by the difficulty of manufacturing large quantities of penicillin and by the rapid renal clearance of the drug necessitating frequent dosing. Penicillins are actively secreted and about 80% of a penicillin dose is cleared within three to four hours of administration. During those times it became common procedure to collect the urine from patients being treated so that the penicillin could be isolated and reused.[4]

This was not a satisfactory solution, however, so researchers looked for a way to slow penicillin secretion. They hoped to find a molecule that could compete with penicillin for the organic acid transporter responsible for secretion such that the transporter would preferentially secrete the competitive inhibitor. The uricosuric agent probenecid proved to be suitable. When probenecid and penicillin are concomitantly administered, probenecid competitively inhibits the secretion of penicillin, increasing its concentration and prolonging its activity. The advent of mass-production techniques and semi-synthetic penicillins solved supply issues, and this use of probenecid declined.[4] Probenecid is still clinically useful, however, for certain infections requiring particularly high concentrations of penicillins.[5]

The chemical structure of penicillin was determined by Dorothy Crowfoot Hodgkin in the early 1940s, enabling synthetic production. A team of Oxford research scientists led by Australian Howard Walter Florey and including Ernst Boris Chain and Norman Heatley discovered a method of mass producing the drug. Florey and Chain shared the 1945 Nobel prize in medicine with Fleming for this work. Penicillin has since become the most widely used antibiotic to date and is still used for many Gram-positive bacterial infections. Alexander Fleming has also discovered that tears have bacteria killing cells in them which cause no physical damage to the body.

Developments from penicillin

The narrow spectrum of activity of the penicillins, along with the poor activity of the orally-active phenoxymethylpenicillin, led to the search for derivatives of penicillin which could treat a wider range of infections.

The first major development was ampicillin, which offered a broader spectrum of activity than either of the original penicillins and allowed doctors to treat a broader range of both and Further development yielded beta-lactmase-resistant penicillins including flucloxacillin, dicloxacillin and methicillin. These were important for their activity against beta-lactamase-

producing bacteria species, but are ineffective against the methicillin-resistant Staphylococcus aureus strains that subsequently emerged.

The line of true penicillins were the antipseudomonal penicillins, such as ticarcillin and piperacillin, useful for their activity against Gram-negative bacteria. However, the usefulness of the beta-lactam ring was such that related antibiotics, including the mecillinams, the carbapenems and, most importantly, the cephalosporins, have at the centre of their structures.

Mode of action

Main article: beta-lactam antibiotic

^{2}-lactam antibiotics work by inhibiting the formation of peptidoglycan cross links in the bacterial cell wall. The ^{2}-lactam moiety of penicillin binds to the enzyme (transpeptidase) that links the peptidoglycan molecules in bacteria, and this weakens the cell wall of the bacterium when it multiplies (in other words, the antibiotic causes cell cytolysis or death when the bacterium tries to divide). Scott Williams is generally credited with having postulated this hypothesis. In addition, the build-up of peptidoglycan precursors triggers the activation of bacterial cell wall hydrolases which further digest the bacteria's existing peptidoglycan.

In addition to the quadraceptics of mechanics, the bacterial wall can break down.

Variants in clinical use

The term “penicillin” is often used generically to refer to one of the narrow-spectrum penicillins, particularly benzylpenicillin.

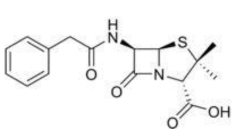
Benzathine benzylpenicillin

Benzathine benzylpenicillin (rINN), also known as *benzathine penicillin*, is slowly absorbed into the circulation, after intramuscular injection, and hydrolysed to benzylpenicillin in vivo. It is the drug-of-choice when prolonged low concentrations of benzylpenicillin are required and appropriate, allowing prolonged antibiotic action over 2–4 weeks after a single IM dose. It is marketed by Wyeth under the trade name *Bicillin L-A*.

Specific indications for benzathine pencillin include: (Rossi, 2004)

- Prophylaxis of rheumatic fever
Early or latent syphilis

Benzylpenicillin (penicillin G)


Penicillin G (Benzylpenicillin)

Benzylpenicillin, commonly known as *penicillin G*, is the gold standard penicillin. Penicillin G is typically given by a parenteral route of administration because it is unstable in the hydrochloric acid of the stomach. Because the drug is given parenterally, higher tissue concentrations of penicillin G can be achieved than is possible with phenoxymethylpenicillin. These higher concentrations translate to increased antibacterial activity.

Specific indications for benzylpenicillin include: (Rossi, 2004)

- Bacterial endocarditis

Meningitis
Aspiration pneumonia, lung abscess
Community-acquired pneumonia
Syphilis
Septicaemia in children

Phenoxymethylpenicillin (penicillin V)

Phenoxymethylpenicillin, commonly known as *penicillin V*, is the orally-active form of penicillin. It is less active than benzylpenicillin, however, and is only appropriate in conditions where high tissue concentrations are not required.

Specific indications for phenoxymethylpenicillin include: (Rossi, 2004)

- Infections caused by Streptococcus pyogenes
  - Tonsilitis

Pharyngitis
Skin infections

- Prophylaxis of rheumatic fever

Moderate-to-severe gingivitis (with metronidazole)

Procaine benzylpenicillin

Procaine benzylpenicillin (rINN), also known as *procaine penicillin*, is a combination of benzylpenicillin with the local anaesthetic agent procaine. Following deep intramuscular injection, it is slowly absorbed into the circulation and hydrolysed to benzylpenicillin — thus it is used where prolonged low concentrations of benzylpenicillin are required.

This combination is aimed at reducing the pain and discomfort associated with a large intramuscular injection of penicillin. It is widely used in veterinary settings.

Specific indications for procaine penicillin include: (Rossi, 2006)

- Syphilis

Respiratory tract infections where compliance with oral treatment is unlikely
Cellulitis, erysipelas

Procaine penicillin is also used as an adjunct in the treatment of anthrax.

Semi-synthetic penicillins

Structural modifications were made to the side chain of the penicillin nucleus in an effort to improve oral bioavailability, improve stability to beta-lactamase activity, and increase the spectrum of action.

Narrow spectrum penicillinase-resistant penicillins

This group was developed to be effective against beta-lactamases produced by Staphylococcus aureus, and are occasionally known as anti-staphylococcal penicillins.

- Methicillin
Dicloxacillin
Flucloxacillin
Oxacillin

Moderate spectrum penicillins

This group was developed to increase the spectrum of action and, in the case of amoxicillin, improve oral bioavailability.

- Amoxicillin

- Ampicillin

Extended Spectrum Penicillins

This group was developed to increase efficacy against Gram-negative organisms. Some members of this group also display activity against Pseudomonas aeruginosa.

- Piperacillin
Ticarcillin
Azlocillin
Carbenicillin

Penicillins with beta-lactamase inhibitors

Penicillins may be combined with beta-lactamase inhibitors to increase efficacy against ^{2}-lactamase-producing organisms. The addition of the beta-lactamase inhibitor does not generally, in itself, increase the spectrum of the partner penicillin.

- Amoxicillin/clavulanic acid

- Ampicillin/sulbactam
Ticarcillin/clavulanic acid
Piperacillin/tazobactam

Adverse effects

Adverse drug reactions

Common adverse drug reactions (e1% of patients) associated with use of the penicillins include: diarrhea, nausea, rash, urticaria, and/or superinfection (including candidiasis). Infrequent adverse effects (0.1–1% of patients) include: fever, vomiting, erythema, dermatitis, angioedema, and/or pseudomembranous colitis.[5]

Pain and inflammation at the injection site is also common for parenterally-administered benzathine benzylpenicillin, benzylpenicillin, and to a lesser extent procaine benzylpenicillin.

Allergy/hypersensitivity

Allergic reactions to any ^{2}-lactam antibiotic may occur in up to 10% of patients receiving that agent. Anaphylaxis will occur in approximately 0.01% of patients.[5] There is perhaps a 5-10% cross-sensitivity between penicillin-derivatives, cephalosporins and carbapenems; but this figure has been challenged by various investigators.

Nevertheless, the risk of cross-reactivity is sufficient to warrant the contraindication of all ^{2}-lactam antibiotics in patients with a history of severe allergic reactions (urticaria, anaphylaxis, interstitial nephritis) to any ^{2}-lactam antibiotic.

See also

- AGG01
- ^{2}-Lactam antibiotic

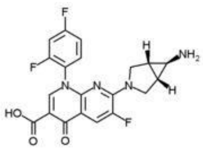
References

1. ^ Fleming A. (1929). "On the antibacterial action of cultures of a penicillium, with special reference to their use in the isolation of B. influenzæ.". Br J Exp Pathol *10* (31): 226–36.

2. ^ **Saxon, W.. "**Anne Miller, 90, first patient who was saved by penicillin**",** *The New York Times***, 1999-06-09.**

3. ^ Krauss K, editor (1999). Yale-New Haven Hospital Annual Report (PDF). Yale-New Haven Hospital.
4. ^ a b Silverthorn, DU. (2004). Human physiology: an integrated approach.. Upper Saddle River (NJ): Pearson Education. ISBN 0-8053-5957-5.
5. ^ a b c (2006) Rossi S, editor Australian Medicines Handbook. Adelaide: Australian Medicines Handbook. ISBN 0-9757919-2-3.

Fluoroquinolone antibiotics



Trovafloxacin

The *quinolones* are a family of broad-spectrum antibiotics. The parent of the group is nalidixic acid. The majority of quinolones in clinical use belong to the subset of *fluoroquinolones*, which have a fluoro group attached the central ring system.

Mechanism

Quinolones and fluoroquinolones are bactericidal drugs, actively killing bacteria. Quinolones inhibit the bacterial DNA gyrase or the topoisomerase IV enzyme, thereby inhibiting DNA replication and transcription. Quinolones can enter cells easily and therefore are often used to treat intracellular pathogens such as Legionella pneumophila and Bacillus anthracis.

Adverse effects

Quinolone antibiotics were once considered relatively safe, but several side effects have become evident with experience. For example, numerous case reports have implicated their use since 1965 in spontaneous tendon ruptures or damage, especially with the concurrent use of a systemic corticosteroid. In the fall of 2004, the Food and Drug Administration upgraded the warnings found within the package inserts for all drugs within this class regarding such serious adverse reactions.

- Peripheral neuropathy (irreversible nerve damage): "Rare cases of sensory or sensor motor axonal polyneuropathy affecting small and or large axons resulting in paresthesias, hypoaesthesias, dysesthesias, and weakness have been reported in patients taking quinolones. Therapy should be discontinued if the patient experiences symptoms of neuropathy including pain, burning, tingling, numbness and or weakness or is found to have deficits in light touch, pain, temperature, position sense, vibratory sensation, and or motor strength in order to prevent the development of an irreversible condition."
- Tendon damage: "Ruptures of the shoulder, hand, Achilles tendon or other tendons that require surgical repair or resulted in prolonged disability have been reported in patients receiving quinolones. Post-marketing surveillance reports indicate that this risk may be increased in patients receiving concomitant corticosteroids, especially the elderly. Fluoroquinolone therapy should be discontinued if the patient experiences pain, inflammation, or rupture of a tendon. Patients should rest and refrain from exercise until diagnosis of tendonitis or tendon rupture had been excluded. Tendon rupture can occur during or after therapy with quinolones."

Other problems include:

- Heart problems (prolonged QT Interval / Torsades de pointes)

Pseudomembranous colitis
Rhabdomyolysis (muscle wasting)
Stevens-Johnson syndrome
Lowered seizure threshold

Resistance

Resistance to quinolones can develop rapidly, even during a course of treatment. Numerous pathogens, including Staphylococcus aureus, enterococci, Pseudomonas aeruginosa, and Streptococcus pyogenes now exhibit resistance worldwide.[1] Widespread veterinary usage of quinolones, particularly in Europe, has been implicated.

Generations

The quinolones are divided into generations based on their antibacterial spectrum. The earlier generation agents are generally more narrow spectrum than the later ones.

1st generation

- cinoxacin (Cinoxacin®)

flumequine (Flubactin®) (*Veterinary use*)
nalidixic acid (NegGam®, Wintomylon®)
oxolinic acid
piromidic acid
pipemidic acid

2nd generation

- ciprofloxacin (Cipro®, Ciproxin®)
- enoxacin (Enroxil®, Penetrex®)

fleroxacin (Megalone®)
levofloxacin (Cravit®, Levaquin®, Quixin®)
lomefloxacin (Maxaquin®)
nadifloxacin
norfloxacin (Noroxin®, Quinabic®, Janacin®)
ofloxacin (Floxin®, Oxaldin®, Tarivid®)
pefloxacin
rufloxacin

3rd generation

- balofloxacin

gatifloxacin (Tequin®)
grepafloxacin (Raxar®)
pazufloxacin Mesilate
sparfloxacin (Zagam®)
temafloxacin
tosufloxacin

4th generation

- clinafloxacin

gemifloxacin (Factive®)
moxifloxacin (Avelox®)
Gatifloxacin (Zymar®)
sitafloxacin
trovafloxacin (Trovan®)

In development

- ecinofloxacin

prulifloxacin

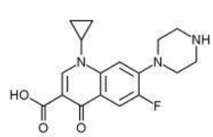
Veterinary use

The quinolones have been widely used in agriculture and several agents exist which have veterinary but not human use.

- danofloxacin (Advocin®, Advocid®) (*Veterinary use*)

difloxacin (Dicural®, Vetequinon®)
enrofloxacin (Baytril®)
marbofloxacin (Marbocyl®, Zenequin®) (*Veterinary use*)
orbifloxacin (Orbax®, Victas®) (*Veterinary use*)
sarafloxacin (Floxasol®, Saraflox®, Sarafin®) (*Veterinary use*)

Ciprofloxacin



Systematic (IUPAC) name

1-cyclopropyl-6-fluoro-4-oxo-7-piperazin-1-yl-quinoline-3-carboxylic acid

Identifiers

CAS number 85721-33-1

ATC code J01**MA02** S01**AX13** S03**AA07**

PubChem 2764

DrugBank APRD00424

Chemical data

Formula C17H18FN3O3

Mol. weight 331.346

Pharmacokinetic data

Bioavailability **69%[1]**

Metabolism Hepatic, including CYP1A2

Half life 4 hours

Excretion Renal

Therapeutic considerations

Pregnancy cat. B3 (Australia), C (USA)

Legal status Schedule 4 (Australia), Prescription Only (UK)

Routes Oral, intravenous, topical (ear drops, eye drops)

Ciprofloxacin is the generic international name for the synthetic antibiotic manufactured and sold by Bayer Pharmaceutical under the brand names *Cipro*® and *Ciproxin*® (and other brand names in other markets, e.g. veterinary drugs), belonging to a group called fluoroquinolones. Ciprofloxacin is bactericidal. Its mode of action depends upon blocking bacterial DNA replication by binding itself to an enzyme called DNA gyrase, thereby preventing the enzyme's ability to untwist the DNA double helix, which is required for DNA replication.

Activity

Ciprofloxacin is a broad-spectrum antibiotic that is active against both Gram-positive and Gram-negative bacteria.

- Enterobacteriaceae

Vibrio

Haemophilus influenzae
Neisseria gonorrhoeae
Neisseria meningitidis
Moraxella catarrhalis
Brucella
Campylobacter
Mycobacterium intracellulare
Legionella sp.
Pseudomonas aeruginosa
Bacillus anthracis - that causes anthrax

Weak activity against:

- Streptococcus pneumoniae

Chlamydia trachomatis
Chlamydia pneumoniae

No activity against:

- Bacteroides

Burkholderia cepacia
Enterococcus faecium
Ureaplasma urealyticum

- and others

The major adverse effect seen with use of is gastrointestinal irritation, common with many antibiotics. Because of its general safety, potency and broad spectrum activity, ciprofloxacin was initially reserved as a "last-resort" drug for use on difficult and drug-resistant infections. As with any antibiotic, however, increasing time and usage has led to an increase in ciprofloxacin-resistant infections, mainly in the hospital setting. Also implicated in the rise of resistant bacteria is the use of lower-cost, less potent fluoroquinolones, and the widespread addition of ciprofloxacin and other antibiotics to the feed of farm animals, which leads to greater and more rapid weight gain, for reasons which are not clear.

In cell culture it is used to treat infection with mycoplasma.

Label information

The drug is available for oral and parenteral use. It is used in lower respiratory infections (pneumonias), urinary tract infections, STDs, septicemias, Legionellosis and atypical Mycobacterioses. Dosage in respiratory infections is 500-1500 mg a day in 2 doses.

It is contraindicated in children, pregnancy, and in patients with epilepsy. Dose adjustment or avoidance may be necessary with liver or renal failure.

Ciprofloxacin can cause photosensitivity reactions and can elevate plasma theophylline levels to toxic values. It can also cause constipation and sensitivity to caffeine. Ciprofloxacin is also known to cause swelling of certain joints and cartilage.

Interactions

Quercetin, a flavonoid occasionally used as a dietary supplement may interact with fluroquinolones, as quercetin competitively binds to bacterial DNA gyrase. Some foods such

as garlic and apples contain high levels of quercetin. Whether this inhibits or enhances the effect of fluoroquinolones is not entirely clear.[2]

Contraindications

Metal cations such as aluminium, magnesium, calcium, ferrous sulfate, and zinc are thought to form chelation complexes with fluoroquinolone antibiotics and prevent the drugs from being absorbed. Because of this, avoid taking antacids which contain aluminium, magnesium or calcium with ciprofloxacin. Sucralfate, which has a high aluminium content, also reduces the bioavailability of ciprofloxacin to approximately 4%[3]. Ciprofloxacin may be taken with meals or on an empty stomach. Ciprofloxacin should not be taken with dairy products or calcium-fortified juices alone, but may be taken with a meal that contains these products.[4]

Heavy exercise is discouraged, as achilles tendon rupture has been reported in patients taking ciprofloxacin. Achilles tendon rupture due to ciprofloxacin use is typically associated with renal failure.

The toxicity of drugs that are metabolised by the cytochrome P450 system is enhanced by concomitant use of some quinolones. They may also interact with the GABA A receptor and cause neurological symptoms; this is further augmented by certain non-steroidal anti-inflammatory drugs.[5]

Fluoroquinolones are increasingly contraindicated for patients who have been to S.E. Asia due to the growing prevalance of antibiotic resistance to the class of antibiotics in that region. [6]

Dosing

Ciprofloxacin is available in oral tablets (250, 500, 650, and 1000 mg), as well as ready-made infusion bottles (200 and 400 mg). A combination preparation of ciprofloxacin 500 mg and tinidazole 600 mg is marketed under the name *Ciplox-TZ®* for infections where anaerobes or protozoa together with ciprofloxacin-sensitive aerobes are likely.

Due to its elimination half-life, ciprofloxacin is administered twice daily. No dose adjustments are generally required for mild to moderate renal impairment.

Business aspects

The discovery and development of ciprofloxacin is that rare case of an actual groundbreaking new drug development, opening up an entire new class of antibiotics for further research, development, and marketing. Even more remarkable, it seems to be a case where the first drug discovered of this class remains the 'gold standard' in terms of efficacy, with the other drugs developed by other pharmaceutical companies relegated to 'me-too' status and forced to compete on the basis of lower cost.

Encouraged by the magnitude of this success, as well as the influx of cash, Bayer Pharmaceutical embarked on a plan to remake itself from a minor pharmaceutical manufacturer into a major player in the international pharmaceutical business, with a lock on the antibiotic field. Unfortunately, a combination of the tendency for antibiotics to be

viewed as a commodity and prescribed on the basis of lowest cost, Bayer's inability to follow up with another 'blockbuster' discovery, and a general downturn in the international pharmaceutical business forced Bayer into a major downsizing in 2000-2001. Faced with the imminent expiry of its patent rights to ciprofloxacin in the early 2000's and the predictable loss of market share to generic ciprofloxacin, Bayer has resorted to the usual strategy of pharmaceutical companies in such a situation; focus on the development and patenting of new variations of the old drug (i.e. pediatric ciprofloxacin, intravenous ciprofloxacin, once-a-day ciprofloxacin, etc.), which will have the side effect of extending the patent on the original drug.

"Cipro" became a household word during the 2001 anthrax attacks after the destruction of the World Trade Center. Bayer took a severe financial blow from the costs involved in rapidly increasing production of the drug to be sold to the American government at far below market price.

Generic ciprofloxacin is now available in many markets around the world including the USA. In addition two new once daily formulations have been launched in the USA. Bayer have marketed Cipro XR which is an extended release formulation. Meanwhile Depomed have developed ProQuin XR another once daily formulation of ciprofloxacin which uses a gastric retention polymer technology to slow the release of ciprofloxacin into the blood.

Ciprofloxacin is the third largest selling molecule in Pakistan pharmaceutical market. It is marketed by numerous companies. In Pakistan, Highnoon Laboratories Ltd. markets the brand under the name "Cyrocin".

Footnotes

1. ^ Drusano GL, Standiford HC, Plaisance K, Forrest A, Leslie J, Caldwell J. Absolute oral bioavailability of ciprofloxacin. Antimicrob Agents Chemother 1986;30:444-6. PMID 3777908.
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4. ^ Drug effects of Ciprofloxacin
5. ^ Brouwers JR. Drug interactions with quinolone antibacterials. Drug Saf 1992;7:268-81. PMID 1524699.
6. ^ Fluoroquinolone Resistance in Neisseria gonorrhoeae -- Colorado and Washington, 1995

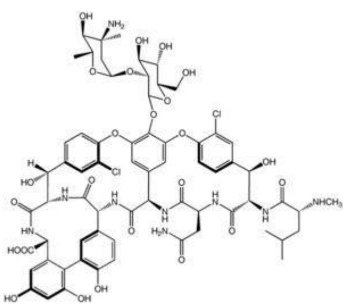
Glycopeptide antibiotics

Glycopeptide antibiotics are a class of antibiotic drugs. They consist of a glycosylated cyclic or polycyclic nonribosomal peptide. Important glycopeptide antibiotics include vancomycin, teicoplanin, ramoplanin, and decaplanin.

This class of drugs inhibit the synthesis of cell walls in susceptible microbes by inhibiting peptidoglycan synthesis. Due to their toxicity, their use is restricted to those patients who are critically ill or who have a demonstrated hypersensitivity to the ²-lactams. Principally effective against gram positive cocci, they exhibit a narrow spectrum of action. They are the last effective line of defense for cases of Methicillin-resistant Staphylococcus aureus.

Vancomycin is usually given intravenously and can cause tissue necrosis and phlebitis at the injection site if given too rapidly. Indeed pain at site of injection is a common adverse event.

Vancomycin



Identifiers

CAS number 1404-90-6

ATC code A07**AA09** J01**XA01**

PubChem 14969

DrugBank APRD01287

Chemical data

Formula $C_{66}H_{75}N_9Cl_2O_{24}$

Mol. weight 1449.3 g.mol^{-1}

Pharmacokinetic data

Bioavailability Negligible (oral)

Metabolism Excreted unchanged

***Half life 4–11 hours** [(adults),](#) **6-10 days** [(adults, impaired renal function)](#)*

Excretion Renal

Therapeutic considerations

Pregnancy cat. B2 (Au), B (U.S.)

Legal status S4 (Au), POM (UK), -only (U.S.)

Routes IV, oral

Vancomycin (INN) (IPA: [ÌvæKkoÈmajsYn]) is a glycopeptide antibiotic used in the prophylaxis and treatment of infections caused by Gram-positive bacteria. It has traditionally been reserved as a drug of "last resort", used only after treatment with other antibiotics had failed, although the emergence of vancomycin-resistant organisms means that it is increasingly being displaced from this role by linezolid and the carbapenems.

It was developed by Eli Lilly, which marketed *vancomycin hydrochloride* under the trade name *Vancocin*. In 2004, Eli Lilly licensed Vancocin to ViroPharma in the U.S., Flynn Pharma in the UK and Aspen Pharmacare in Australia. The patent expired in the early 1980s and generic versions of the drug are also available under various trade names.

Pharmacology and chemistry

It is a branched tricyclic glycosylated nonribosomal peptide produced by the fermentation of the Actinobacteria species Amycolatopsis orientalis (formerly designated [Nocardia orientalis](#)).

Vancomycin acts by inhibiting proper cell wall synthesis in Gram-positive bacteria. The mechanism inhibited, and various factors related to entering the outer membrane of Gram-negative organisms mean that vancomycin is not active against Gram-negative bacteria (except some non-gonococcal species of Neisseria).

Specifically, vancomycin prevents incorporation of N-acetylmuramic acid (NAM)- and N-acetylglucosamine (NAG)-peptide subunits into the peptidoglycan matrix; which forms the major structural component of Gram-positive cell walls.

The large hydrophilic molecule is able to form hydrogen bond interactions with the terminal D-alanyl-D-alanine moieties of the NAM/NAG-peptides. Normally this is a five-point interaction. This binding of vancomycin to the D-Ala-D-Ala prevents the incorporation of the NAM/NAG-peptide subunits into the peptidoglycan matrix.

Vancomycin exhibits atropisomerism — it has two chemically distinct rotamers owing to the rotational restriction of the chlorotyrosine residue (on the right hand side of the figure).

The form present in the drug is the thermodynamically more stable conformer, and, importantly, has more potent activity.

Clinical use

Indications

Vancomycin is indicated for the treatment of serious, life-threatening infections by Gram-positive bacteria which are unresponsive to other less toxic antibiotics.

The increasing emergence of vancomycin-resistant enterococci has resulted in the development of guidelines for use by the Centers for Disease Control (CDC) Hospital Infection Control Practices Advisory Committee. These guidelines restrict use of vancomycin to the following indications:[1]

- treatment of serious infections caused by susceptible organisms resistant to penicillins (methicillin-resistant Staphylococcus aureus and multi-resistant Staphylococcus epidermidis (MRSE)) or in individuals with serious allergy to penicillins
- pseudomembranous colitis (relapse or unresponsive to metronidazole treatment)
- For treatment of infections caused by gram-positive microorganisms in patients who have serious allergies to beta-lactam antimicrobials. (http://wonder.cdc.gov/wonder/prevguid/m0039349/m0039349.asp)
- antibacterial prophylaxis for endocarditis following certain procedures in penicillin-hypersensitive individuals at high risk
- surgical prophylaxis for major procedures involving implantation of prostheses in institutions with a high rate of MRSA or MRSE

Adverse effects

Common adverse drug reactions (e1% of patients) associated with IV vancomycin include: local pain, which may be severe and/or thrombophlebitis. Nephrotoxicity is an infrequent adverse effect (0.1–1% of patients). Rare adverse effects (<0.1% of patients) include: anaphylaxis, toxic epidermal necrolysis, erythema multiforme, red man syndrome (see below), superinfection, thrombocytopenia, neutropenia, leucopenia, tinnitus, dizziness and/or ototoxicity (see below).[1]

Dosing considerations

Intravenous vs oral administration

Vancomycin needs to be given intravenously (IV) for systemic therapy since it does not cross through the intestinal lining. It is a large hydrophilic molecule which partitions poorly across the gastrointestinal mucosa. The only indication for oral vancomycin therapy is in the

treatment of pseudomembranous colitis, where it must be given orally to reach the site of infection in the colon.

Red man syndrome

Vancomycin must be administered in a dilute solution slowly, over at least 60 minutes (maximum rate of 10 mg/minute for doses >500 mg).[1] This is due to the high incidence of pain and thrombophlebitis and to avoid an infusion reaction known as the *red man syndrome* or *red neck syndrome*. This syndrome, usually appearing within 4–10 minutes after the commencement or soon after the completion of an infusion, is characterised by flushing and/or and an erythematous rash that affects the face, neck and upper torso. Less frequently, hypotension and angioedema may also occur. Symptoms may be treated with antihistamines, including diphenhydramine.[2]

Therapeutic drug monitoring

Vancomycin activity is considered to be time-dependent – that is, antimicrobial activity depends on the duration that the drug level exceeds the minimum inhibitory concentration (MIC) of the target organism. Thus, peak levels have not been shown to correlate with efficacy or toxicity – indeed concentration monitoring is unnecessary in most cases. Circumstances where therapeutic drug monitoring (TDM) is warranted include: patients receiving concomitant aminoglycoside therapy, patients with (potentially) altered pharmacokinetic parameters, patients on haemodialysis, during high dose or prolonged treatment, and patients with impaired renal function. In such cases, trough concentrations are measured.[1][3][4][5]

Toxicity

Vancomycin has traditionally been considered a nephrotoxic and ototoxic drug, based on observations by early investigators of elevated serum levels in renally impaired patients who had experienced ototoxicity, and subsequently through case reports in the medical literature. However, as the use of vancomycin increased with the spread of MRSA beginning in the seventies, it was recognised that the previously reported rates of toxicity were not being observed. This was attributed to the removal of the impurities present in the earlier formulation of the drug, although those impurities were not specifically tested for toxicity.

Nephrotoxicity

Subsequent reviews of accumulated case reports of vancomycin-related nephrotoxicity found that many of the patients had also received other known nephrotoxins, particularly aminoglycosides. Most of the rest had other confounding factors, or insufficient data regarding the possibility of such, that prohibited the clear association of vancomycin with the observed renal dysfunction.

In 1994, Cantu and colleagues found that the use of vancomycin monotherapy was clearly documented in only three of 82 available cases in the literature.[3] Prospective and retrospective studies attempting to evaluate the incidence of vancomycin-related nephrotoxicity have largely been methodologically flawed and have produced variable results. The most methodologically sound investigations indicate that the actual incidence of vancomycin-induced nephrotoxicity is around 5–7%. To put this into context, similar rates of renal dysfunction have been reported for cefamandole and benzylpenicillin, two reputedly non-nephrotoxic antibiotics.

Additionally, evidence to relate nephrotoxicity to vancomycin serum levels is inconsistent. Some studies have indicated an increased rate of nephrotoxicity when trough levels exceed 10 µg/mL, but others have not reproduced these results. Nephrotoxicity has also been observed with concentrations within the "therapeutic" range as well. Essentially, the reputation of vancomycin as a nephrotoxin is over-stated, and it has not been demonstrated that maintaining vancomycin serum levels within certain ranges will prevent its nephrotoxic effects, when they do occur.

Ototoxicity

Attempts to establish rates of vancomycin-induced ototoxicity are even more difficult due to the scarcity of quality evidence. The current consensus is that clearly related cases of vancomycin ototoxicity are rare. The association between vancomycin serum levels and ototoxicity is also uncertain. While cases of ototoxicity have been reported in patients whose vancomycin serum level exceeded 80 µg/mL, cases have been reported in patients with therapeutic levels as well. Thus, it also remains unproven that therapeutic drug monitoring of vancomycin for the purpose of maintaining "therapeutic" levels will prevent ototoxicity.

Interactions with other nephrotoxins

Another area of controversy and uncertainty concerns the question of whether, and if so, to what extent, vancomycin increases the toxicity of other nephrotoxins. Clinical studies have yielded variable results, but animal models indicate that there probably is some increased nephrotoxic effect when vancomycin is added to nephrotoxins such as aminoglycosides. However, a dose- or serum level-effect relationship has not been established.

Antibiotic resistance

Microbial resistance to vancomycin is a growing problem, particularly within health care facilities such as hospitals. With vancomycin being the last-line antibiotic for serious Gram-positive infections there is the growing prospect that resistance will result in a return to the days when fatal bacterial infections were common. Vancomycin-resistant enterococci (VRE) emerged in 1987. Vancomycin-resistance emerged in more common pathogenic organisms during the 1990s and 2000s, including vancomycin-intermediate Staphylococcus aureus (VISA), vancomycin-resistant Staphylococcus aureus (VRSA), and vancomycin-resistant Clostridium difficile.[6][7] There is some suspicion that agricultural use of avoparcin,

another similar glycopeptide antibiotic, has contributed to the emergence of vancomycin-resistant organisms.

One mechanism of resistance to vancomycin appears to be alteration to the terminal amino acid residues of the NAM/NAG-peptide subunits, normally D-alanyl-D-alanine, which vancomycin binds to. Variations such as D-alanyl-D-lactate and D-alanyl-D-serine result in only a 4-point hydrogen bonding interaction being possible between vancomycin and the peptide. This loss of just one point of interaction results in a 1000-fold decrease in affinity.

In Enterococci this modification appears to be due to the expression of an enzyme which alters the terminal residue. Three main resistance variants have been characterised to date among resistant Enterococcus faecium and E. faecalis populations.

- VanA - resistance to vancomycin and teicoplanin, inducible on exposure to these agents
- VanB - lower level resistance, inducible by vancomycin but strains may remain susceptible to teicoplanin
- VanC - least clinically important, resistance only to vancomycin, constitutive resistance

The development and use of novel antibiotics such as linezolid and daptomycin is expected to delay, but not halt, the emergence of bacteria resistant to all available antibiotics.

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See also

- Antibiotic resistance

Glycylcycline antibiotics

Glycylcyclines are a new class of antibiotics derived from tetracycline. These tetracycline analogues are specifically designed to overcome two common mechanisms of tetracycline resistance, namely resistance mediated by acquired efflux pumps and/or ribosomal protection. Presently, there is only one glycylcycline antibiotic for clinical use: tigecycline.

History

The development of these agents was spurred by the increasing prevalence of bacteria resistant to tetracyclines. These agents were first synthesized in the early 1990's by making modifications to the tetracyclines. By adding a bulky N,N-dimethylglycylamido side chain to position 9 of minocycline, the compound became less susceptible to tetracycline resistance mediated by acquired efflux pumps and/or ribosomal protection. Further development of this initial work led to the creation of tigecycline, the first glycylcycline available for clinical use.

Mechanism of Action

Glycylcycline antibiotics have a similar mechanism of action as tetracycline antibiotics. Both classes of antibiotics bind to the 30S ribosomal subunit to prevent the amino-acyl tRNA from binding to the A site of the ribosome. However, the glycylcyclines appear to bind more effectively than the tetracyclines [1].

Mechanisms of Resistance

While glycylcyclines have greater efficacy against organisms with tetracycline resistance mediated by acquired efflux pumps and/or ribosomal protection, the glycylcyclines are not effective against organisms with chromosomal efflux pumps, such as Pseudomonas and Proteeae [2].

Side Effects and Contraindications

Since glycylcyclines are similar to tetracyclines, they share many of the same side effects and contraindications as tetracyclines. These side effects may include nausea/vomiting, headache, photosensitivity, discoloration of growing teeth, and fetal damage.

These antibiotics should not be given to pregnant women due to risk of fetal harm. Additionally, these drugs should not be administered during periods of tooth development

because of the risk of tooth discoloration. Due to glycylcyclines' similarities with tetracyclines, hypersensitivity reactions to tetracycline antibiotics may predispose one to hypersensitivity reactions with glycylcycline antibiotics; hence, glycylcyclines should be used with caution in these patients.

References

- Tigecycline: A novel glycylcycline antiobiotic. Aug 1, 2005. By: Kara L. Smith, BSc, Sarah M. McCabe, BSc, Jeffrey R. Aeschlimann, PharmD. Formulary.

Lincosamide antibiotics

Lincosamides (eg. lincomycin, clindamycin) are a class of drugs which bind to 50S subunit of bacterial ribosomes and inhibit early elongation of peptide chain by inhibiting transpeptidase reaction. In this sense they have a similar action to macrolides.

Resistance

Target bacteria may alter the drug's target site (similar to resistance found in macrolides and streptogramins). Also, enzymatic inactivation of clindamycin has been described (rare).

Pharmacodynamics

These are bacteriostatic drugs and antagonists of macrolides and streptogramins.

Further reading

- Van Bambeke F. Mechanisms of action. In Armstrong D, Cohen J. Infectious diseases. Mosby, London, 1999, pp7/1.1-7/1.14

Nitroimidazole antibiotics

Nitroimidazoles are imidazole heterocycles with a nitro group that have been used to combat anaerobic bacterial and parasitic infections. Perhaps the most common example is metronidazole (*Flagyl* ®). Other heterocycles such as nitrothiazoles (thiazole) are also used for this purpose. Nitroheterocycles may be reductively activated in hypoxic cells, and then undergo redox recycling or decompose to toxic products.

References

- Annu. Rev. Pharmacol. Toxicol. 1989. 29:165~7

Polyketide antibiotics

Polyketides are secondary metabolites from bacteria, fungi, plants, and animals. Secondary metabolites seem to be unnecessary for an organism's ontogeny, but appear to have applications such as defence and intercellular communication. Polyketides are derived from the polymerization of acetyl and propionyl subunits in a similar process to fatty acid synthesis. They also serve as building blocks for a broad range of natural products or are derivatized.

Polyketides are structurally a very diverse family of natural products with an extremely broad range of biological activities and pharmacological properties. Polyketide antibiotics, antifungals, cytostatics, anticholesterolemics, antiparasitics, coccidiostatics, animal growth promotants and natural insecticides are in commercial use.

Examples

- Macrolides
    - Picromycin, the first isolated macrolide (1950).
    - **The** antibiotics erythromycin B**,** clarithromycin**, and azithromycin.**
    - The immunosuppressant tacrolimus (FK506).
- **Polyene** antibiotics
    - Amphotericin.
- Tetracyclines
    - The tetracycline family of antibiotics.
- Others
    - Discodermolide

Biosynthesis

The biosynthesis of polyketides shares striking similarities with the fatty acid biosynthesis. Polyketides are synthesized by one or more specialized polyketide-synthase (PKS) enzyme. The PKS genes for a certain polyketide are usually organized in one operon in bacteria and in gene clusters in eukaryotes. The type I polyketide-synthases are large, highly modular proteins, while type II polyketide-synthases are aggregates of monofunctional proteins.

Each type I polyketide-synthase module consists of several domains with defined functions, separated by short spacer regions. The order of modules and domains of a complete polyketide-synthase is as follows (in the order N-terminus to C-terminus):

- Starting or loading module: AT-ACP-
- Elongation or extending modules: -KS-AT-[DH-ER-KR]-ACP-
- Termination or releasing module: -TE

Domains:

- AT: Acyl-transferase
- ACP: Acyl carrier protein with an SH group on the cofactor, a serine-attached 4'-Phosphopantetheine
- KS: Keto-synthase with an SH group on a cysteine side-chain
- KR: Keto-reductase
- DH: Dehydratase
- ER: Enoyl-reductase
- TE: Thio-esterase

The polyketide chain and the starter groups are bound with their carboxy group to the SH groups of the ACP and the KS domain through a thioester linkage: R-C(=O)OH + HS-protein <=> R-C(=O)S-protein + H2O. The growing chain is handed over from one SH group to the next by trans-acylations and is releases at the end by hydrolysis or by cyclization (alcoholysis or aminolysis).

Starting stage:

- The starter group, usually acetyl-CoA or malonyl-CoA, is loaded onto the ACP domain of the starter module catalyzed by the starter module's AT domain.

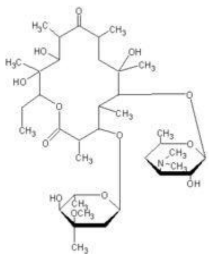
Elongation stages:

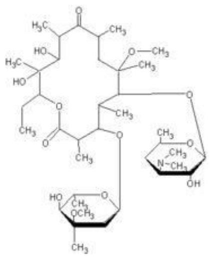
- The polyketide chain is handed over from the ACP domain of the previous module to the KS domain of the current module, catalyzed by the KS domain.
- The elongation group, usually malonyl-CoA or methyl-malonyl-CoA, is loaded onto the current ACP domain catalyzed by the current AT domain.
- The ACP-bound elongation group reacts in a Claisen condensation with the KS-bound polyketide chain under CO2 evolution, leaving a free KS domain and an ACP-bound elongated polyketide chain. The reaction takes place at the KS***n***-bound end of the chain, so that the chain moves out one position and the elangation group becomes the new bound group.
- Optionally, the new fragment of the polyketide chain can be altered stepwise by additional domains. The KR (keto-reductase) domain reduces the ^{2}-keto group to a ^{2}-hydroxy group, the DH (dehydratase) domain splits off H2O, resulting in the ±-^{2}-unsaturated alkene, and the ER (enoyl-reductase) domain reduces the ±-^{2}-double-bond to a single-bond.
- This cycle is repeated for each elongation module.

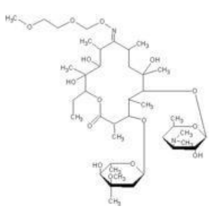
Termination stage:

- The TE (thio-esterase) domain hydrolyzes the completed polyketide chain from the ACP-domain of the previous module.

Macrolide antibiotics


Erythromycin. The macrolide ring is the lactone (cyclic ester) at upper left.


Clarithromycin


Roxithromycin

The *macrolides* are a group of drugs (typically antibiotics) whose activity stems from the presence of a macrolide ring, a large lactone ring to which one or more deoxy sugars, usually cladinose and desosamine, are attached. The lactone ring can be either 14, 15 or 16-membered. Macrolides belong to the polyketide class of natural products.

Members

Commonly prescribed Macrolides

- erythromycin
    - azithromycin (Zithromax®)
- clarithromycin **(Biaxin®)**
    - dirithromycin (Dynabac®)
    - roxithromycin (Rulid®, Surlid®)

Developmental Macrolides

- carbomycin A
josamycin

kitasamycin
oleandomycin
spiramycin
troleandomycin
tylosin/tylocine (Tylan®)

Ketolides

Ketolides are a new class of antibiotics that are structurally related to the macrolides. They are used to fight respiratory tract infections caused by macrolide-resistant bacteria.

- telithromycin (Ketek®)

cethromycin

Others are: spiramycin (used for treating toxoplasmosis), ansamycin, oleandomycin, carbomycin and tylocine.

Non-antibiotic macrolides

The drug Tacrolimus, which is used as an immunosuppressant, is also a macrolide. It has similar activity to cyclosporin.

Toxic macrolide

- mycolactone

Uses

Macrolides are used to treat infections such as respiratory tract infections and soft tissue infections. The antimicrobial spectrum of macrolides is slightly wider than that of penicillin, and therefore macrolides are a common substitute for patients with a penicillin allergy. Beta-hemolytic streptococci, pneumococci, staphylococci and enterococci are usually susceptible to macrolides. Unlike penicillin, macrolides have been shown to be effective against mycoplasma, mycobacteria, some rickettsia and chlamydia.

Mechanism of action

The mechanism of action of the macrolides is inhibition of bacterial protein synthesis by binding reversibly to the subunit 50S of the bacterial ribosome, thereby inhibiting translocation of peptidyl-tRNA. This action is mainly bacteriostatic, but can also be bactericidal in high concentrations. Macrolides tend to accumulate within leukocytes, and are therefore actually transported into the site of infection.

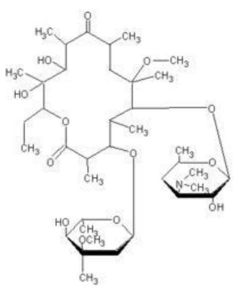
- A novel, non-antibiotic, anti-inflammatory effect of 14-membered macrolides was discovered in Japan(Kudo S. et al.), which is especially effective in improving control of diffuse panbronchiolitis(DPB). Research on the anti-inflammatory properties of the macrolide ring is ongoing.

Resistance

The primary means of bacterial resistance to macrolides occurs by post-transcriptional methylation of the of the 23S bacterial ribosome. This acquired resistance can be either plasmid-mediated or chromosomal, i.e through mutation, and results in cross-resistance to macrolides, lincosamides, and streptogramins (an MLS-resistant phenotype).

Two other types of acquired resistance rarely seen include the production of drug-inactivating enzymes (esterases or kinases) as well as the production of active ATP-dependent efflux proteins that transport the drug outside of the cell.

Clarithromycin



Systematic (IUPAC) name

6-(4-dimethylamino-3-hydroxy- 6-methyl-tetrahydropyran-2-yl) oxy-14-ethyl-12,13-dihydroxy- 4-(5-hydroxy-4-methoxy-4,6- dimethyl-tetrahydropyran-2-yl) oxy-7-methoxy-3,5,7,9,11, 13-hexamethyl-1- oxacyclotetradecane-2,10-dione

Identifiers

CAS number 81103-11-9

ATC code J01**FA09**

PubChem 84029

DrugBank APRD00181

Chemical data

Formula C***38***H***69***NO***13***

Mol. weight 747.953 g/mol

Pharmacokinetic data

Bioavailability **50%**

Protein binding low binding

Metabolism hepatic

Half life 3-4 hours

Therapeutic considerations

Pregnancy cat. C (USA), B3 (Aus)

Routes oral

Clarithromycin is a macrolide antibiotic used to treat pharyngitis, tonsillitis, acute maxillary sinusitis, acute bacterial exacerbation of chronic bronchitis, pneumonia (especially atypical pneumonias associated with Chlamydia pneumoniae or TWAR), skin and skin structure infections, and, in HIV and AIDS patients to prevent, and to treat, disseminated Mycobacterium avium complex or MAC. In addition, it is sometimes used to treat Legionellosis.

Clarithromycin is available under several brand names, for example *Biaxin*, *Klacid*, and *Claripen*.

History

Clarithromycin was invented by scientists at the Japanese drug company Taisho Pharmaceutical in the 1970s. The product had emerged through efforts to develop a version of the antibiotic erythromycin that did not experience acid instability in the digestive tract and thereby cause side effects, such as nausea and stomach ache. Taisho filed for patent protection over its new drug around 1980 and subsequently introduced a branded version of its drug, called Clarith, to the Japanese market in 1991. In 1985 Taisho had partnered with the American company Abbott Laboratories for the international rights, and Abbott also gained FDA approval for Biaxin in October 1991. The drug went generic in Europe in 2004 and in the U.S. in mid-2005.

Potential new uses

The Australian biotechnology company Giaconda is working on a new triple drug therapy for Crohn's disease that combines clarithromycin with rifabutin and clofazimine.

Available forms

Clarithromycin is commonly administered in tablets (Biaxin®), extended-release tablets (Biaxin XL®), or oral suspension. In the United States generic clarithromycin is available from Andrx, Genpharm, Ivax, Ranbaxy Laboratories, Roxane, Sandoz, Teva and Wockhardt.

Mechanism of action

Clarithromycin prevents bacteria from growing, by interfering with their protein synthesis. Clarithromycin binds to the subunit 50S of the bacterial ribosome, and thus inhibits the translocation of peptides. Clarithromycin has similar antimicrobial spectrum as erythromycin, but is more effective against certain gram-negative bacteria, particularly Legionella pneumophilae. Besides this bacteriostatic effect, clarithromycin also has bactericidal effect on certain strains such as Haemophilus influenzae, Streptococcus pneumoniae and Neisseria gonorrhoeae.

Pharmacokinetics

Unlike erythromycin, clarithromycin is acid-stable and can therefore be taken orally without being protected from gastric acids. It is readily absorbed, and diffused into most tissues and phagocytes. Due to the high concentration in phagocytes, clarithromycin is actively transported to the site of infection. During active phagocytosis, large concentrations of clarithromycin is released. The concentration of clarithromycin in the tissues can be over 10 times higher than in plasma. Highest concentrations were found in liver and lung tissue.

Metabolism

Clarithromycin has a fairly rapid first-pass hepatic metabolism, i.e it is metabolised by the liver. However, this metabolite, 14-hydroxy clarithromycin is almost twice as active as clarithromycin. The half-life of clarithromycin is about 5 hours and 14-hydroxy clarithromycin's about 7 hours. Clarithromycin's and its metabolites' main routes of elimination are urinary and biliary excretion.

Side effects

Most common side-effects are gastrointestinal: diarrhea, nausea, abdominal pain and vomiting. Less common side-effects include headaches, rashes, alteration in senses of smell and taste. Dry mouth, anxiety, hallucinations, and nightmares have also been reported. In more serious cases it has been known to cause jaundice, other liver disorders, and kidney problems including kidney failure. Inform your doctor immediately if side effects are extremely bothersome or serious.

Special precautions

Allergic reactions can occur with clarithromycin use. People with a history of allergy, asthma, hay fever or hives seem to be more susceptible to these reactions. The reaction can be immediate and severe.

Allergic symptoms include wheezing, hives, itching, swelling, spasms in the throat and breathing tubes, swelling of the face and neck, joint and muscle pain, difficulty breathing, fever and skin rashes. Rashes can range in severity, the most serious cases being toxic

epidermal necrolysis and Stevens-Johnson syndrome. Nausea and vomiting are not symptoms of an allergic reaction.

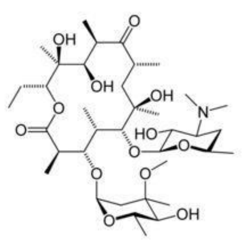
Contraindications

Clarithromycin should be used with caution if the patient has liver or kidney disease, certain heart problems (e.g., QTc prolongation or bradycardia), or a mineral imbalance (e.g., low potassium or magnesium levels). Many drugs interact with clarithromycin: be sure to carefully read the information sheet to make sure you are not currently taking one that might adversely react.

External links

- Biaxin Official web site by Abbott Laboratories

Erythromycin



Systematic (IUPAC) name

6-(4-dimethylamino-3-hydroxy-6-methyl-oxan-2-yl)oxy-14-ethyl-7,12,13-trihydroxy-

4-(5-hydroxy-4-methoxy-4,6-dimethyl-oxan-2-yl)oxy-3,5,7,9,11,13-hexamethyl- 1-oxacyclotetradecane-2,10-dione
Identifiers

CAS number 114-07-8

ATC code J01**FA01**

PubChem 3255

DrugBank APRD00953

Chemical data

Formula $C_{37}H_{67}NO_{13}$

Mol. weight 733.93 g/mol

Pharmacokinetic data

Bioavailability **100%**

Protein binding 90%

Metabolism liver (under 5% excreted unchanged)

Half life 1.5 hours

Excretion bile

Therapeutic considerations

Pregnancy cat. $A_{(AU)}$ $B_{(US)}$

Legal status P*rescription only*

Routes oral, iv, im

Erythromycin (also known as *eryth ethylsuc*) is a macrolide antibiotic which has an antimicrobial spectrum similar to or slightly wider than that of penicillin, and is often used for people who have an allergy to penicillins. For respiratory tract infections, it has better coverage of atypical organisms, including mycoplasma. It is also used to treat outbreaks of chlamydia, syphilis, acne and gonorrhea. Structurally, this macrocyclic compound contains a 14-membered lactone ring with ten asymmetric centers and two sugars (L-cladinose and D-desoamine), making it a compound very difficult to produce via synthetic methods.

Erythromycin is produced from a strain of the actinomyces Saccaropolyspora erythraea, formerly known as Streptomyces erythraeus.

History

Abelardo Aguilar, a Filipino scientist, sent some soil samples to his employer Eli Lilly in 1949. Eli Lilly's research team, led by J. M. McGuire, managed to isolate Erythromycin from the metabolic products of a strain of Streptomyces erythreus (designation changed to "Saccharopolyspora erythraea") found in the samples. Lilly filed for patent protection of the compound and U.S. patent 2,653,899 was granted in 1953. The product was launched commercially in 1952 under the brand name *Ilosone*® (after the Philippine region of Iloilo where it was originally collected from). Erythromycin was formerly also called *Ilotycin*®. In 1981, Nobel laurate (1965 in chemistry) and Professor of Chemistry at Harvard University (Cambridge, MA) Robert B. Woodward and a large team of researchers reported the first stereocontrolled asymmetric chemical synthesis of Erythromycin A.

The antiobiotic clarithromycin was invented by scientists at the Japanese drug company Taisho Pharmaceutical in the 1970s as a result of their efforts to overcome the acid instability of erythromycin.

Available forms

Erythromycin is available in enteric-coated tablets, slow release capsules, oral suspensions, ophthalmic solutions, ointments, gels and injections.

Brand names include Robimycin, E-Mycin, E.E.S. Granules, E.E.S.-200, E.E.S.-400, E.E.S.-400 Filmtab, Erymax, Ery-Tab, Eryc, Erypar, EryPed, Eryped 200, Eryped 400, Erythrocin Stearate Filmtab, Erythrocot, E-Base, Ilosone, MY-E, Pediamycin, Zineryt and PCE Dispertab.

Mechanism of action

Erythromycin prevents bacteria from growing by interfering with their protein synthesis. Erythromycin binds to the 23s rRNA molecule in the 50S of the bacterial ribosome, blocking the exit of the growing peptide chain thus inhibiting the translocation of peptides.

Pharmacokinetics

Erythromycin is easily inactivated by gastric acids, therefore all orally administered formulations are given as either enteric coated or as more stable salts or esters. Erythromycin is very rapidly absorbed, and diffused into most tissues and phagocytes. Due to the high concentration in phagocytes, erythromycin is actively transported to the site of infection, where during active phagocytosis, large concentrations of erythromycin are released.

Metabolism

Most of erythromycin is metabolised by demethylation in the liver. Its main elimination route is in the bile, and a small portion in the urine. Erythromycin's half-life is 1.5 hours.

Side-effects

Gastrointestinal disturbances such as diarrhea, nausea, abdominal pain and vomiting are fairly common so it tends not to be prescribed as a first-line drug. However, erythromycin may be useful in treating gastroparesis due to this pro-motility effect. Intravenous erythromycin may also be used in endoscopy as an adjunct to clear gastric contents.

More serious side-effects, such as reversible deafness are rare. Allergic reactions, while uncommon, may occur, ranging from urticaria to anaphylaxis. Cholestasis, Stevens-Johnson syndrome and toxic epidermal necrolysis are some other rare side effects that may occur.

Erythromycin has been shown to increase the probability of pyloric stenosis in children whose mothers took the drug during the late stages of pregnancy or while nursing.

Contraindications

Earlier case reports on sudden death prompted a study on a large cohort that confirmed a link between erythromycin, ventricular tachycardia and sudden cardiac death in patients also taking drugs that prolong the metabolism of erythromycin (like verapamil or diltiazem) by interfering with CYP3A4 (Ray et al 2004). Hence, erythromycin should not be administered in patients using these drugs, or drugs that also prolong the QT time. Other examples include terfenadine (Seldane, Seldane-D), astemizole (Hismanal), cisapride (Propulsid, withdrawn in many countries for prolonging the QT time) and pimozide (Orap).

Some people can be allergic to Erythromycin and a small dose can cause massive liver failure.

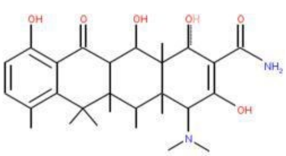
References

- Ray WA, Murray KT, Meredith S, Narasimhulu SS, Hall K, Stein CM. Oral Erythromycin and the Risk of Sudden Death from Cardiac Causes. N Engl J Med 2004;351:1089-96.
- British National Formulary "BNF 49" March 2005.

External links

- U.S. Patent 2,653,899

Tetracycline antibiotics



The 4 rings of the basic tetracycline structure.

Tetracyclines are a group of broad-spectrum antibiotics whose general usefulness has been reduced with the onset of bacterial resistance. Despite this, they continue to remain the treatment of choice for some specific indications.

They are so named for their four (“tetra-”) hydrocarbon rings (“-cycl-”) derivation (“-ine”).

History

The first member of the group to be discovered was Chlortetracycline (Aureomycin) in the late 1940s by Dr. Benjamin Duggar, a scientist employed by Lederle Laboratories who derived the substance from a golden-colored, fungus-like, soil-dwelling bacterium named Streptomyces aureofaciens. Oxytetracycline (Terramycin) was discovered shortly afterwards by AC Finlay et al, it came from a similar soil bacterium named Streptomyces rimosus. Robert Burns Woodward determined the structure of Oxytetracycline enabling Lloyd H. Conover to successfully produce tetracycline itself as a synthetic product. The

development of many chemically altered antibiotics formed this group. In June 2005, tigecycline, the first member of a new subgroup of tetracyclines named glycylcyclines was introduced to treat infections which are resistant to other antimicrobics including conventional Tetracyclines.

Examples of tetracyclines

- Naturally-occurring
  - Tetracycline
  - Chlortetracycline
  - Oxytetracycline
  - Demeclocycline
- Semi-synthetic
  - Doxycycline
  - Lymecycline
  - Meclocycline
  - Methacycline
  - Minocycline
  - Rolitetracycline

Tigecycline may also be considered a tetracycline antibiotic, though it is usually classified as a glycylcycline antibiotic.

Indication

Tetracyclines may be used in the treatment of infections of the respiratory tract, sinuses, middle ear, urinary tract, intestines, and also gonorrhoea, especially in patients allergic to ^{2}-lactams and macrolides; however, their use for these indications is less popular than it once was due to widespread resistance development in the causative organisms.

Their most common current use is in the treatment of moderately severe acne and rosacea (tetracycline, oxytetracycline, doxycycline or minocycline).

Doxycycline is also used as a prophylactic treatment for infection by Bacillus anthracis (anthrax) and is effective against Yersinia pestis, the infectious agent of bubonic plague. It is also used for malaria treatment and prophylaxis, as well as treating elephantiasis.

They remain the treatment of choice for infections caused by chlamydia (trachoma, psittacosis, salpingitis, urethritis and L. venereum infection), Rickettsia (typhus, Rocky Mountain spotted fever), brucellosis, and spirochetal infections (borreliosis, syphilis, and Lyme disease). In addition, they may be used to treat anthrax, plague, tularemia, and Legionnaires' disease.

They may have a role in reducing the duration and severity of cholera, although drug-resistance is occurring[1] and their effects on overall mortality is questioned.[2]

Demeclocycline has an additional use in the treatment of SIADH.

Tetracycline derivatives are currently being investigated for the treatment of certain inflammatory disorders.

Administration

When ingested, it is usually recommended that tetracyclines should be taken with a full glass of water two hours after eating, and one hour before eating. This is partly due to the fact that tetracycline binds easily with magnesium, aluminium, iron, and calcium, which reduces its ability to be completely absorbed by the body. Dairy products or preparations containing iron are not recommended directly after taking the drug.

Cautions

Tetracyclines should be used with caution in those with liver impairment and may worsen renal failure (except doxycycline and minocycline). They may increase muscle weakness in myasthenia gravis and exacerbate systemic lupus erythematosus. Antacids and milk reduce the absoption of tetracyclines.

Like many antibiotics, they decrease the effectiveness of birth control pills.

Drugs in the tetracycline class become toxic over time, so expired prescriptions of these drugs should be discarded after the expiration date has passed.

Contraindications

Tetracycline use should be avoided in pregnant or lactating women, and in children with developing teeth because they may result in permanent staining (dark yellow-gray teeth with a darker horizontal band that goes across the top and bottom rows of teeth), and possibly affect the growth, of teeth and bones.

Side effects

Side effects from tetracyclines are not always common, but of particular note is possible photosensitive allergic reaction which increases the risk of sunburn under exposure to UV light from the sun or other sources. This may be of particular importance for those intending to take on holidays long-term doxycyline as a malaria prophylaxis.

They may cause stomach or bowel upsets, and rarely allergic reactions. Very rarely severe headache and vision problems may be signs of dangerous secondary intracranial hypertension also known as Pseudotumor cerebri.

Mechanism and resistance

Tetracycline inhibits cell growth by inhibiting translation. It binds to the 16S part of the 30S ribosomal subunit and prevents the amino-acyl tRNA from binding to the A site of the ribosome. The binding is reversible in nature.

Cells become resistant to tetracycline by at least three mechanisms: enzymatic inactivation of tetracycline, efflux and ribosomal protection. Inactivation is the rarest type of

resistance, where an acetyl group is added to the molecule, causing inactivation of the drug. In efflux, a resistance gene encodes a membrane protein that actively pumps tetracycline out of the cell. This is the mechanism of action of the tetracycline resistance gene on the artificial plasmid pBR322. In Ribosomal protection a resistance gene encodes a protein which can have several effects depending on what gene is transferred. Six classes of ribosomal protection genes/proteins have been found, all with high sequence homology suggesting a common evolutionary ancestor. Possible mechanisms of action of these protective proteins include: 1) blocking tetracyclines from binding to the ribosome, 2) binding to the ribosome and distorting the structure to still allow t-RNA binding while tetracycline is bound, and 3) binding to the ribosome and disloding tetracycline. All of these changes to ribosomes are reversible (non-covalent) because ribosomes isolated from both tetracycline resistant and susceptible organisms both bind tetracycline equally well in vitro.

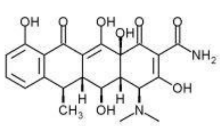
References

1. ^ Bhattacharya SK, National Institute of Cholera and Enteric Diseases (2003). "An evaluation of current cholera treatment". Expert Opin Pharmacother *4* (2): 141-6. PMID 12562304.
2. ^ Parsi VK (2001). "Cholera". Prim. Care Update Ob Gyns *8* (3): 106-109. PMID 11378428.
    - British National Formulary 49 March 2005

See also

- Glycylcycline

Doxycycline



Systematic (IUPAC) name

(2-(amino-hydroxy-methylidene)-4-dimethylamino

-5,10,11,12a-tetrahydroxy-6-methyl- 4a,5,5a,6-tetrahydro-4H-tetracene-1,3,12-trione
Identifiers

CAS number 564-25-0

ATC code J01**AA02**

PubChem 11256

DrugBank APRD00597

Chemical data

Formula $C_{22}H_{24}N_2O_8$

Mol. weight 444.435 g/mol

Pharmacokinetic data

Bioavailability **100%**

Metabolism hepatic

Half life 18-22 hours

Excretion urine, feces

Therapeutic considerations

Pregnancy cat. D(US)

Legal status POM(UK) -only(US)

Routes oral, periodontal, iv, im

Doxycycline (INN) (IPA: [ÌdRksjÈsajklin]) is a member of the tetracycline antibiotics group and is commonly used to treat a variety of infections. Brand names include Monodox®, Periostat®, Vibramycin®, Vibra-Tabs®, Doryx®, Vibrox®, Adoxa®, Doxyhexal® and Atridox® (topical doxycycline hyclate for gum disease).

Indicated uses

As well as the general indications for all members of the tetracycline antibiotics group, Doxycycline is frequently used to treat chronic prostatitis, sinusitis, syphilis, chlamydia, pelvic inflammatory disease, acne and rosacea. In addition it is used in the treatment and prophylaxis of Bacillus anthracis (anthrax) and malaria. Its mechanism of action against malaria is to specifically impair in the progeny the apicoplast genes resulting in their abnormal cell division.[1]

It is also effective against Yersinia pestis (the infectious agent of bubonic plague) and is prescribed for the treatment of Lyme disease and Rocky Mountain spotted fever.

Elephantiasis is a disease caused by a nematode (worm) Wuchereria bancrofti. It causes swollen limbs and genitals (Filariasis) and affects over 120 million people in the world. Previous anti-nematode treatments have been limited by poor levels of effectiveness, drug side effects and high costs. Doxycycyline was shown in 2003 to kill the symbiotic Wolbachia bacteria upon which the nematodes are dependent.[2] Field trials in 2005 showed that

Doxycycline almost completely eliminates blood-borne filaria when given for an 8 week course.[3][4]

Cautions and Side effects

Are as for other members of the tetracycline antibiotics group. However the 10% risk of photosensitivity skin reactions is of particular importance for those intending long-term use for malaria prophylaxis. Reports of GERD have been cited with the use of Doxycycline.

Unlike some other members of the group, it may be used in those with renal impairment.

Doxycycline impairs the effectiveness of many types of contraceptive pill and physicians recommend the use of barrier contraception for people taking the drug to prevent unwanted pregnancy. Contrary to popular belief, the drug does not cause patients to exhibit side-effects preventing other forms of sexual activity such as oral or anal sex.

It should be taken with a full glass of water to prevent irritation of the esophagus or stomach.

Experimental applications

At subantimicrobial doses, doxycycline is an inhibitor of matrix metalloproteinases, and has been used in various experimental systems for this purpose. Doxycycline has been used successfully in the treatment of one patient with lymphangioleiomyomatosis, an otherwise progressive and fatal disease.[5]

Doxycycline has also been used to regulate transgene expression in mice using the Tet-on gene control system.

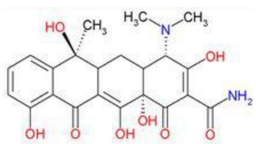
References and notes

1. ^ Dahl E, Shock J, Shenai B, Gut J, DeRisi J, Rosenthal P (Sep 2006). "Tetracyclines specifically target the apicoplast of the malaria parasite Plasmodium falciparum.". Antimicrob Agents Chemother *50* (9): 3124-31. PMID 16940111.
2. ^ Hoerauf A, Mand S, Fischer K, Kruppa T, Marfo-Debrekyei Y, Debrah AY, Pfarr KM, Adjei O, Buttner DW (2003). "Doxycycline as a novel strategy against bancroftian filariasis-depletion of Wolbachia endosymbionts from Wuchereria bancrofti and stop of microfilaria production". Med Microbiol Immunol (Berl) *192* (4): 211-6. PMID 12684759.
3. ^ Taylor MJ, Makunde WH, McGarry HF, Turner JD, Mand S, Hoerauf A (2005). "Macrofilaricidal activity after doxycycline treatment of Wuchereria bancrofti: a double-blind, randomised placebo-controlled trial". Lancet *365* (9477): 2116-21. PMID 15964448.

4. ^ **Outland, Katrina. "**New Treatment for Elephantitis: Antibiotics**",** ***The Journal of Young Investigators*****, 2005 Volume 13.**

5. ^ Moses MA, Harper J, Folkman J (2006). "Doxycycline treatment for lymphangioleiomyomatosis with urinary monitoring for MMPs". N Engl J Med *354* (24): 2621–22.
   - British National Formulary 45 March 2003

Tetracycline



Systematic (IUPAC) name

2-(amino-hydroxy-methylidene)-4-dimethylamino-6,10,11,12a-tetrahydroxy-6-methyl-4,4a,5,5a-tetrahydrotetracene-1,3,12-trione
OR
4-(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,6,10,12,12a-pentahydroxy-1,11dioxo-naphthacene-2carboxamide

Identifiers

CAS number 60-54-8

ATC code A01**AB13** D06**AA04** J01**AA07** S01**AA09** S02**AA08** S03**AA02**

PubChem 643969

DrugBank APRD00572

Chemical data

Formula $C_{22}H_{24}N_2O_8$

Mol. weight 444.435 g/mol

Pharmacokinetic data

Bioavailability

60-80% Oral, while fasting

<40% Intramuscular

Metabolism Not metabolised

Half life 6-11 hours

Excretion Fecal and Renal

Therapeutic considerations

Pregnancy cat. $D_{(AU)}$ $D_{(US)}$

Legal status Prescription only

Routes oral, topical (skin & eye), im, iv

Tetracycline (INN) (IPA: [Ìt[trYÈsajklin]) is a broad-spectrum antibiotic produced by the streptomyces bacterium, indicated for use against many bacterial infections. It is commonly used to treat acne. It is sold under the brand names *Sumycin®;*, *Tetracyn®;* and *Panmycin®*, among others. *Actisite®* is a thread-like fiber form, used in dental applications. It is also used to produce several semi-synthetic derivatives, which together are known as the Tetracycline antibiotic group. It works by inhibiting action of the prokaryotic 30S ribosome. Toxicity may be result of inactivation of mitochondrial 30S ribosomes in host cells.

History

Tetracycline was first discovered by Lloyd Conover in the research departments of Pfizer. The patent for Tetracycline was first issued in 1950 (patent number 2,624,354). Tetracycline sparked the development of many chemically altered antibiotics and in doing so has proved to be one of the most important discoveries made in the field of antibiotics.

Cautions, Contraindications, Side effects

Are as those of the Tetracycline antibiotics group:

- Can stain developing teeth (even when taken by the mother during pregnancy)

Inactivated by Ca^{2+} ion, not advised to be taken with milk or yogurt
Skin photosensitivity, not advised to be exposed to the Sun or intense light
Drug induced lupus, and hepatitis
Tinnitus

Indication

Tetracycline's primary use is for the treatment of acne vulgaris and rosacea.

It is also used to treat a very wide range of infections; see Tetracycline antibiotics for details.

Other uses

Since tetracycline is absorbed into bone, it is used as a marker of bone growth for biopsies in humans, and as a biomarker in wildlife to detect consumption of medicine- or vaccine-containing baits. The presence of tetracyline in bone is detected by its fluorescence.

Polymyxin antibiotics

Polymyxins are cationic detergent antibiotics, with a general structure of a cyclic peptide with a long hydrophobic tail. They disrupt the structure of the bacterial cell membrane by interacting with its phospholipids. Polymyxins have a bactericidal effect on Gram-negative bacilli, especially on pseudomonas and coliform organisms. Polymyxin antibiotics are highly neurotoxic and nephrotoxic, and very poorly absorbed from the gastrointestinal tract.

Well known examples:

- Colistin
Polymyxin B
Surfactin

Polymyxin acts as an antibiotic by damaging the cytoplasmic membrane of bacteria. Also polymyxins biological source is Bacillius polymyxa.

Polypeptide antibiotics - Lantibiotics

Lantibiotics are a class of peptide antibiotics that contain polycyclic thioether amino acids as well as the unsaturated amino acids dehydroalanine and 2-aminoisobutyric acid. These characteristic cyclic thioether amino acids are composed of either lanthionine or methyllanthionine. Lantibiotics are produced by a large number of Gram positive bacteria such as Streptococcus and Streptomyces to attack other gram positive bacteria and as such they are considered a member of the bacteriocins.

History

[1]The name Lantibiotics was introduced in 1988 as an abbreviation for "Lanthionine-containing peptide antibiotics". The first structures of these antimicrobial agents were first produced by pioneering work by Gross and Morell in the late sixties and early seventies, thus marking the formal intorduction of Lantibiotics. Since then Lantibiotics such as Nisin have been used auspiciously for food preservation and have yet to encounter significant bacterial

resistance. These attributes of lantibiotics have lead to more detailed research into their structures and biosynthetic pathways.

Classification

- Type A Lantibiotics are long flexible molecules - eg Nisin, subtilin, epidermin. Subgroup AI includes Mutacin II, subgroup AII includes Mutacin I & III.
- Type B Lantibiotics are globular - eg mersacidin, actagardin, cinnamycin.

See Brotz and Sahl. JAC (2000) 46, 1-6 for discussion of mechanism of action. (Type A kill rapidly by pore formation, type B inhibit peptidoglycan biosynthesis)

Mechanism of action

Lantibiotics show substantial specificity for some components (eg lipid II) of bacterial cell membranes especially of Gram positive bacteria. They are active in very low concentrations.

Application

[2]Lantibiotics are produced by Gram-positive bacteria and show strong antimicrobial action towards a wide range of other Gram-positive bacteria. As such they have become attractive candidates for use in food preservation (by inhibiting pathogens that cause food spoilage) and the pharmaceutical industry (to prevent or fight infections in humans or animals). See C. van Kraaij et al, Nat. Prod. Rep. (1999), 16, 583 - 584 for more detailed disccusion of the pharmaceutical application of lantibiotics.

References

- 1. W. van der Donk et al. Chem. Rev. (2005) 105, 633 - 683
- 2. C. van Kraaij et al, Nat. Prod. Rep. (1999), 16, 575 - 587.

Rifamycin antibiotics

The *rifamycins* are a group of antibiotics which are synthesized either naturally by the bacterium Amycolatopsis mediterranei, or artificially. Rifamycins are particularly effective against mycobacteria, and are therefore used to treat tuberculosis, leprosy, and mycobacterium avium complex (MAC) infections.

The rifamycin group includes the "classic" rifamycin drugs as well as the rifamycin derivatives Rifampicin, Rifabutin and Rifapentine.

The bacterium

Streptomyces mediterranei was first isolated in 1957 from a soil sample collected near the beachside town of St Raphael in southern France. The name was originally given by two microbiologists working with the Italian drug company Group Lepetit SpA in Milan, the Italian Grazia Beretta and Pinhas Margalith of Israel.

In 1969 the bacterium was renamed Nocardia mediterranei when another scientist named Thiemann found that it had a cell wall typical of the Nocardia species. Then in 1986 the bacterium was renamed again as Amycolatopsis mediterranei, as the first species of a new genus, because a scientist named Lechevalier discovered that the cell wall lacked mycolic acid and was not able to be infected by the Nocardia and Rhodococcus phages.

The classic rifamycin drugs

Rifamycins were first isolated in 1957 from a fermentation culture of Streptomyces mediterranei at the laboratory of Gruppo Lepetit SpA in Milan by a scientist named Piero Sensi, working with the Israeli scientist Pinhas Margalith. Eventually around seven rifamycins were discovered, named Rifamycin A, B, C, D, E, S and SV.

Of the various rifamycins Rifamycin B was first introduced commercially. Lepetit filed for patent protection of Rifamycin B in the UK in August 1958 and in the US in March 1959. The British patent GB921045 was granted in March 1963 and U.S. Patent 3,150,046 was granted in September 1964. The drug is widely regarded as having helped conquer the issue of drug-resistant tuberculosis in the 1960s.

The rifamycin derivatives

Lepetit introduced Rifampicin, an orally active rifamycin, around 1966. Rifabutin, a derivative of rifamycin S, was invented around 1975 and came on to the US market in 1993. Hoechst Marion Roussel (now part of Aventis) introduced rifapentine in 1999.

Rifaximin is a oral rifamycin marketed in the US by Salix Pharmaceuticals that is not absorbed from the intestine. It is intended to treat intestinal infections due to Escherichia coli.

Currently available rifamycins

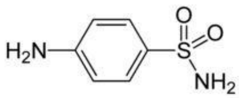
- Rifampicin
Rifabutin
Rifapentine
Rifaximin

References

- Sensi. et al., Farmaco Ed. Sci. (1959) 14, 146-147 - the paper announcing the discovery of the rifamycins.

- Thieman et al. Arch. Microbiol. (1969), 67 147-151 - the paper which renamed Streptomyces mediterranei as Nocardia mediterranei.
- Lechevalier et al., Int. J. Syst. Bacteriol. (1986), 36, 29) - the paper which renamed Nocardia mediterranei as Amycolatopsis mediterranei.

Sulfonamide antibiotics



Sulfonamide (medicine) *Systematic (IUPAC) name*

sulfanilamide

Identifiers

CAS number 63-74-1

ATC code **J01**EB06 **D06**BA05

PubChem 5333

DrugBank APRD00438

Chemical data

Formula C***6***H***8***N***2***O***2***S

Mol. weight 172.206 g/mol

There are several *sulphonamide*-based groups of drugs. The original *antibacterial sulfonamides* (sometimes called simply *sulfa drugs*) are synthetic antimicrobial agents that contain the sulfonamide group. The *sulfonylureas* (main article: sulfonylureas) and *thiazide diuretics* (main article thiazide) are newer drug groups based on the antibacterial sulfonamides.

In bacteria, antibacterial sulfonamides act as competitive inhibitors of the enzyme dihydropteroate synthetase, DHPS. DHPS catalyses the coversion of PABA (para-aminobenzoate) to dihydropteroate, a key step in folate synthesis. Folate is necessary for the cell to synthesize nucleic acids (nucleic acids are essential building blocks of DNA and RNA), and in its absence cells will be unable to divide. Hence the sulfonamide antibacterials exhibit a bacteriostatic rather than bactericidal effect.

Folate is not synthesized in mammalian cells, but is instead a dietary requirement. This explains the selective toxicity to bacterial cells of these drugs.

Sulfa allergies are common, hence medications containing sulfonamides are prescribed carefully.

History

Sulfonamide drugs (known widely as "sulfa drugs") were the first antibacterial antibiotics, and paved the way for the antibiotic revolution in medicine. The first sulfonamide was trade named Prontosil, which is a prodrug. Experiments with Prontosil began in 1932 in the laboratories of the Bayer Corporation, a component of the huge German chemical trust IF Farben. The dye-based drug was synthesized by Bayer chemist Josef Klarer and tested in animals under the direction of physician/researcher Gerhard Domagk. Domagk quickly won the 1939 Nobel Prize in Medicine and Physiology, an honor that Hitler forbade him to accept (Hitler was incensed at the awarding of a Nobel Peace Prize a few years earlier to an anti-Nazi activist). Domagk's Prize also caused some bad feeling between him and Klarer. The discovery was in fact a team effort in which Domagk played a central role, operating under the general direction of Heinrich Hoerlein, a Farben executive later tried (and acquited) at Nuremberg. The first official communication about the breakthrough discovery was not published until 1935, more than two years after the drug was patented by Klarer and his research partner Fritz Mietzsch. Prontosil was the first medicine ever discovered that could effectively treat a range of bacterial infections inside the body. It had a strong protective action against infections caused by streptococci, including blood infections, childbed fever, and erysipelas, and a lesser effect on infections caused by other cocci. Perplexingly, it had no effect at all in the test tube, exerting its antibacterial action only in live animals. Later it was discovered by a French research team at the Pasteur Institute that the drug was metabolized into two pieces inside the body, releasing from the inactive dye portion a smaller, colorless, active compound called sulfanilamide. The discovery helped establish the concept of "bioactivation" and dashed the German corporation's dreams of enormous profit; the active molecule sulfanilamide (or sulfa) had first been synthesized in 1906 and was widely used in the dye-making industry; its patent had since expired and the drug was available to anyone.

The result was a sulfa craze. For several years in the late 1930s hundreds of manufacturers produced tens of thousands of tons of myriad forms of sulfa. Unfortunately one of them, a preparation called Elixir Sulfanilamide, was made with a toxic solvent, diethylene glycol. The Elixir killed more than one hundred people, mostly children, in the US, and led to the passage of the 1938 Food, Drug, and Cosmetic Act. As the first and only only effective antibiotic available in the years before penicillin, sulfa drugs continued to thrive through the early years of World War II, saving the lives of Winston Churchill, Franklin Delano Roosevelt's son, and tens of thousands of patients. Sulfa had a central role in preventing wound infections during the war. American soldiers were issued a first aid kit containing sulfa powder and were told to sprinkle it on any open wound. During the years 1942 to 1943, Nazi doctors conducted sulfanilamide experiments on prisoners in concentration camps.

The sulfanilamide compound is more active in the protonated form, which in case of the acid works better in a basic environment. The solubility of the drug is very low and sometimes can crystalize in the kidneys, due to its first pK***a*** of around 10. This is a very painful experience so patients are told to take the medication with copious amounts of water. Newer compounds have a pK***a*** of around 5-6 so the problem is avoided.

Many thousands of molecules containing the sulfanilamide structure have been created since its discovery (by one account, over 5400 permutations by 1945), yielding improved formulations with greater effectiveness and less toxicity. Sulfa drugs are still widely used for

conditions such as acne and urinary tract infections, and are receiving renewed interest for the treatment of infections caused by bacteria resistant to other antibiotics.

Sulpha is an alternate (UK English) spelling of the common name for Sulfonamide antibiotics.

Preparation

Sulfonamides are prepared by the reaction of a sulfonyl chloride with ammonia or an amine. Certain sulfonamides (sulfadiazine or sulfamethoxazole) are sometimes mixed with the drug trimethoprim, which acts against dihydrofolate reductase.

Side Effects

Sulfonamides have the potential to cause a variety of untoward reactions, including urinary tract disorders, haemopoietic disorders, porphyria and hypersensitivity reactions. When used in large dose, it may develop a strong allergic reaction.

See also

- Antibiotic

Antibiotic resistance

Antibiotic resistance is the ability of a microorganism to withstand the effects of an antibiotic. Antibiotic resistance can develop naturally via natural selection through random mutation. SOS response of low-fidelity polymerases can also cause mutation via a process known as programmed evolution. Once such a gene is generated, bacteria can then transfer the genetic information in a horizontal fashion (between individuals) by plasmid exchange. If a bacterium carries several resistance genes, it is called *multiresistant* or, informally, a *superbug*.

Antibiotic resistance can also be introduced artificially into a microorganism through transformation protocols. This can be a useful way of implanting artificial genes into the microorganism.

Causes

Antibiotic resistance is a consequence of evolution via natural selection or programmed evolution. The antibiotic action is an environmental pressure; those bacteria which have a mutation allowing them to survive will live on to reproduce. They will then pass this trait to their offspring, which will be a fully resistant generation.

Several studies have demonstrated that patterns of antibiotic usage greatly affect the number of resistant organisms which develop. Overuse of broad-spectrum antibiotics, such as second- and third-generation cephalosporins, greatly hastens the development of methicillin resistance, even in organisms that have never been exposed to the selective pressure of methicillin per se (thus the resistance was already present). Other factors contributing towards resistance include incorrect diagnosis, unnecessary prescriptions, improper use of antibiotics by patients, and the use of antibiotics as livestock food additives for growth promotion.

Mechanisms of antibiotic resistance

The four main mechanisms by which microorganisms exhibit resistance to antimicrobials are:

1. Drug inactivation or modification: e.g. enzymatic deactivation of Penicillin G in some penicillin-resistant bacteria through the production of ^{2}-lactamases.
2. Alteration of target site : e.g. alteration of PBP - the binding target site of penicillins - in MRSA and other penicillin-resistant bacteria.

3. Alteration of metabolic pathway: e.g. some sulfonamide-resistant bacteria do not require para-aminobenzoic acid (PABA) - an important precursor for the synthesis of folic acid and nucleic acids in bacteria inhibited by sulfonamides. Instead, like mammalian cells, they turn to utilizing preformed folic acid.
4. Reduced drug accumulation: by decreasing drug permeability and/or increasing active efflux on the cell surface.

Resistant pathogens

Staphylococcus aureus (colloquially known as "Staph aureus") is one of the major resistant pathogens. Found on the mucous membranes and the skin of around a third of the population, it is extremely adaptable to antibiotic pressure. It was the first bacterium in which penicillin resistance was found -- in 1947, just four years after the drug started being mass-produced. Methicillin was then the antibiotic of choice. MRSA (methicillin-resistant Staphylococcus aureus) was first detected in Britain in 1961 and is now "quite common" in hospitals. MRSA was responsible for 37% of fatal cases of blood poisoning in the UK in 1999, up from 4% in 1991. Half of all S. aureus infections in the US are resistant to penicillin, methicillin, tetracycline and erythromycin.

This left vancomycin as the only effective agent available at the time. However, VRSA (Vancomycin-resistant Staphylococcus aureus) was first identified in Japan in 1997, and has since been found in hospitals in England, France and the US. VRSA is also termed GISA (glycopeptide intermediate Staphylococcus aureus) or VISA (vancomycin insensitive Staphylococcus aureus), indicating resistance to all glycopeptide antibiotics.

A new class of antibiotics, oxazolidinones, became available in the 1990s, and the first commercially available oxazolidinone, linezolid, is comparable to vancomycin in effectiveness against MRSA. Linezolid-resistance in Staphylococcus aureus was reported in 2003.

Enterococcus faecium is another superbug found in hospitals. Penicillin-Resistant Enterococcus was seen in 1983, Vancomycin-Resistant Enterococcus (VRE) in 1987, and Linezolid-Resistant Enterococcus (LRE) in the late 1990s.

Penicillin-resistant pneumonia (or pneumococcus, caused by Streptococcus pneumoniae) was first detected in 1967, as was penicillin-resistant gonorrhea. Resistance to penicillin substitutes is also known as beyond S. aureus. By 1993 Escherichia coli was resistant to five fluoroquinolone variants. Mycobacterium tuberculosis is commonly resistant to isoniazid and rifampin and sometimes universally resistant to the common treatments. Other pathogens showing some resistance include Salmonella, Campylobacter, and Streptococci.

In November, 2004, the Centers for Disease Control and Prevention (CDC) reported an increasing number of Acinetobacter baumannii bloodstream infections in patients at military medical facilities in which service members injured in the Iraq/Kuwait region during Operation Iraqi Freedom and in Afghanistan during Operation Enduring Freedom were treated. Most of these showed multidrug resistance (MRAB), with a few isolates resistant to all drugs tested. [1]

Antibiotic resistance and the role of animals

MRSA is acknowledged to be a human commensal and pathogen. MRSA has been found in cats, dogs and horses, where it can cause the same problems as it does in humans. Owners can transfer the organism to their pets and vice-versa, and MRSA in animals is generally believed to be derived from humans.

This is not the case for other pathogens, however. There are concerns that some antibiotic resistant organisms may derive from the use of antibiotics in food animals. 15% of all antibiotics manufactured in Europe are used on animals. For precisely this reason, in many countries, antibiotics that are licensed for human use are banned from use in animals. However, related antibiotics are often used as growth promoters and to prevent or treat illnesses (particularly in poultry) and have been associated with the development of resistant strains in bacteria isolated from poultry and other food animals.

The US Food and Drug Administration banned enrofloxacin from use in poultry in July 2005 in response to concerns that use of enrofloxacin use in chickens might contribute to ciprofloxacin resistance in Campylobacter infecting humans. The US Food and Drug Administration felt that serious questions could be raised about whether use of enrofloxacin posed zero risk to humans. Although the risk to humans may be zero, this is not currently proved with scientific certainty. Campylobacter is an avian gut commensal, and Campylobacter gastroenteritis in humans is sometimes associated with the consumption of undercooked chicken, although handling of raw chicken and preparation and consumption of chicken in the home have also been associated with reduced risks of Campylobacter infections. Campylobacter resistance is up to 20% in parts of the developed world. Enrofloxacin is a fluoroquinolone whose mechanism of action is very similar to ciprofloxacin; it is used in veterinary practice to treat respiratory infections of poultry, when it is added to water or to the feed and may be used to medicate a whole flock. Scientists and lobbyists have often pointed out that there is no evidence of the transfer of antibiotic resistance in food animals to humans, but given that Campylobacter does not naturally occur in humans (unless they eat foods with campylobacter) and that ciprofloxacin resistance has increased among people who travel to countries with widespread abuse of ciprofloxacin, it has been tempting for advocates who oppose consumption of meat and/or use of animal antibiotics to conclude that ciprofloxacin-resistant Campylobacter in humans could arise from eating chicken contamined with enrofloxacin-resistant Campylobacter, despite the lack of scientific evidence. Indeed in countries where fluoroquinolone use is restricted, fluoroquinolone resistance in Campylobacter is uncommon.[1] Sadly, a preoccupation with fear of resistance has led many scientists and regulators to overlook the fact that appropriate use of antibiotics in animal feeds can reduce human exposures to susceptible bacteria. For example, in Australia, where enrofloxacin is not used, ciprofloxacin resistance rates in human isolates are relatively low (comparable to historical rates reported among domestically acquired cases of campylobacteriosis in the United States, but much smaller than rates in Spain, Thailand, and other countries where ciprofloxacin is over-used). However, rates of campylobacteriosis in the population are many time greater than in the United States. It remains to be seen whether the 2005 ban on enrofloxacin in the United States will be

followed by increases in campylobacteriosis rates -- a possibility that FDA declined to consider in arguing for a ban.

The illegal use of amantadine to medicate poultry in the South of China and other parts of southeast Asia, means that although the H5N1 strain that appeared in Hong Kong in 1997 was amantadine sensitive, the more recent strains have all been amantadine resistant. This seriously reduces the treatment options available to doctors in the event of an influenza pandemic.

Eighteen UK organisations banded together in November 1997 to set guidelines on the use of antibiotics in farm animals, in order to address the concerns of the larger public. The consortium is called RUMA (Responsible use of Medicine in Agriculture Alliance) Members of this consortium include the British Poultry Council and various industry and pharmaceutical firms. The European Union has banned the use of all antibiotics as growth promoters since 1 January 2006.

Alternatives to antibiotics

Prevention

Washing hands properly reduces the chance of getting infected or spreading infection. Thoroughly washing or avoiding of raw foods such as fruits, vegetables, raw eggs, and undercooked meat can also reduce the chance of an infection.

Vaccines

Vaccines do not suffer the problem of resistance because a vaccine enhances the body's natural defenses, while an antibiotic operates separately from the body's normal defenses. Nevertheless, new strains may evolve that escape immunity induced by vaccines.

While theoretically promising, anti-staphylococcal vaccines have shown limited efficacy, because of immunological variation between Staphylococcus species, and the limited duration of effectiveness of the antibodies produced. Development and testing of more effective vaccines is under way.

Phage therapy

Phage therapy is a more recent alternative that can cope with the problem of resistance.

Development of newer antibiotics

The resistance problem demands that a renewed effort be made to seek antibacterial agents effective against pathogenic bacteria resistant to current antibiotics. One of the possible strategies towards this objective is the rational localization of bioactive phytochemicals. Plants have an almost limitless ability to synthesize aromatic substances, most of which are phenols or their oxygen-substituted derivatives such as tannins. Most are secondary metabolites, of which at least 12,000 have been isolated, a number estimated to

be less than 10% of the total. In many cases, these substances serve as plant defense mechanisms against predation by microorganisms, insects, and herbivores. Many of the herbs and spices used by humans to season food yield useful medicinal compounds including those having antibacterial activity.

Traditional healers have long used plants to prevent or cure infectious conditions. Many of these plants have been investigated scientifically for antimicrobial activity and a large number of plant products have been shown to inhibit growth of pathogenic bacteria. A number of these agents appear to have structures and modes of action that are distinct from those of the antibiotics in current use, suggesting that cross-resistance with agents already in use may be minimal.

Applications

Antibiotic resistance is an important tool for genetic engineering. By constructing a plasmid which contains an antibiotic resistance gene as well as the gene being engineered or expressed, a researcher can ensure that when bacteria replicate, only the copies which carry along the plasmid survive. This ensures that the gene being manipulated passes along when the bacteria replicates.

The most commonly used antibiotics in genetic engineering are generally "older" antibiotics which have largely fallen out of use in clinical practice. These include:

- ampicillin
    - kanamycin
- tetracycline
    - chloramphenicol

Industrially the use of antibiotic resistance is disfavored since maintaining bacterial cultures would require feeding them large quantities of antibiotics. Instead, the use of auxotrophic bacterial strains (and function-replacement plasmids) is preferred.

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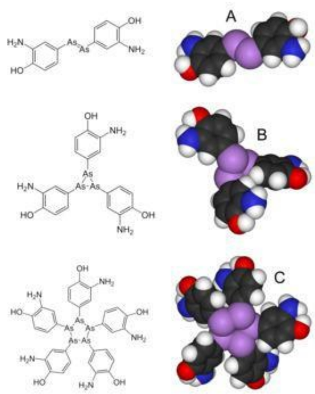
1. ^ Brierley R (2006). "Fluoroquinolone use should be curbed in animals". Lancet Infect Dis *6* (6): 329.

Arsphenamine

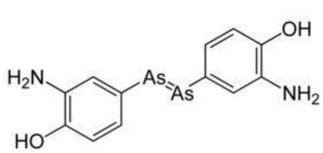

The structure of *arsphenamine* was believed to be *A* until 2005, when new research suggested the true structure was in fact a mixture of the trimer *B* and the pentamer *C*

Arsphenamine is a drug that was used to treat syphilis and trypanosomiasis. It was the first modern chemotherapeutic agent. Sahachiro Hata discovered the anti-syphilitic activity of this compound in 1908 in the laboratory of Paul Ehrlich, during a survey of hundreds of newly-synthesized organic arsenical compounds. Ehrlich had theorized that by screening many compounds a drug could be discovered with anti-microbial activity. Ehrlich's team began their search for such a magic bullet among chemical derivatives of the dangerously-toxic drug atoxyl. This was the first organized team effort to optimize the biological activity of a lead compound through systematic chemical modifications, the basis for nearly all modern pharmaceutical research.

Arsphenamine was marketed under the trade name *Salvarsan* in 1910. It was also called *606*, because it was the 606th compound synthesized for testing. Salvarsan was the first organic anti-syphillitic, and a great improvement over the inorganic mercury compounds that had been used previously. A more soluble (but slightly less effective) arsenical compound, Neosalvarsan, (neoarsphenamine), became available in 1912. These arsenical compounds came with considerable risk of side effects, and they were supplanted as treatments for syphilis in the 1940s by penicillin.

The bacterium that causes syphilis is a spirochete, Treponema pallidum. Arsphenamine is not toxic to spirochetes until it has been converted to an active form by the body, so the discovery of this drug could not have been made without Hata's animal testing. After leaving Erlich's laboratory, Hata continued parallel investigation of the new medicine in Japan.[1]

The structure was believed to be:



However, in 2005, researchers determined Arsphenamine's structure to be a compound of a cyclic trimer and a pentamer.

References

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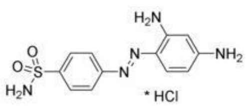
2. Yarnell, A. (2005) Salvarsan 'Chemical and Engineering News' 83(25).

Prontosil



Systematic (IUPAC) name

4-[(2,4-diaminophenyl)azo]benzenesulfonamide

Identifiers

CAS number 103-12-8

Chemical data

Formula C***12***H***13***N***5***O***2***S - HCl

Mol. weight 291.33

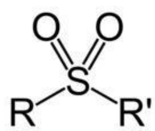
Therapeutic considerations

Routes oral

Prontosil, the first commercially available antibiotic, was developed by a research team at the Bayer Laboratories in Germany. Its discovery and development opened a new era in medicine. The molecule, first synthesized by Bayer chemists Josef Klarer and Fritz Mietzsch, was tested and found effective against some important bacterial infections in mice by Gerhard Domagk, who subsequently received the 1939 Nobel Prize in Medicine. Prontosil was the result of five years of research and testing involving thousands of chemical substances. The definitive tests were done in 1932, but results were not published until 1935, after I.G. Farben had obtained a patent. It was quickly found by a French research team at the Pasteur Institute that Prontosil, a nearly insoluble red azo dye, is broken down in the body, releasing a much simpler, colorless molecule sulfanilimide through a process called

"bioactivation." Sulfanilamide, the active portion of the Prontosil molecule, was out of patent, cheap to produce, easy to link into other molecules, and soon widely available in hundreds of forms. As a result, Prontosil failed to make the profits in the marketplace hoped for by Bayer. Although quickly eclipsed by newer sulfa drugs and, in the mid-1940s and through the 1950s, penicillin and a string of newer antibiotics that proved more effective against more types of bacteria, Prontosil remained on the market until the 1960s. Prontosil's discovery ushered in the era of antibiotics and had a profound impact on pharmaceutical research, drug laws, and medical history.

Sulfone


The structure of the sulfonyl group

A *sulfone* is a chemical compound containing a sulfonyl functional group attached to two carbon atoms. The central sulfur atom is twice double bonded to oxygen and has two further hydrocarbon substituents. The general structural formula is R-S(=O)(=O)-R' where R and R' are the organic groups. The use of the alternative name *sulphone* is discouraged by IUPAC. Sulfides are often the starting materials for sulfones by organic oxidation through the intermediate formation of sulfoxides. For example dimethyl sulfide is oxidized to dimethyl sulfoxide and then to dimethyl sulfone.

In the Ramberg-Bäcklund Reaction and the Julia olefination sulfones are converted to alkenes.

A sulfone can also be any of various organic sulfur compounds having a sulfonyl group attached to two carbon atoms, especially such a compound formerly used as an antibiotic to treat leprosy, dermatitis herpetiformis, tuberculosis, or Pneumocystis Carinii Pneumonia (PCP).

Antifungals

An *antifungal drug* is medication used to treat fungal infections such as athlete's foot, ringworm and candidiasis (thrush), as well as serious systemic infections like cryptococcal meningitis. Such drugs can be either prescription drugs or OTC drugs.

List of antifungal drugs

Antifungals work by exploiting differences between mammalian and fungal cells to kill off the fungal organism without significantly harming the host. Unlike bacteria, both fungi and humans are eukaryotes. The basic structure of fungal cells and human cells is nearly identical. This means it is more difficult to find a target for an antifungal medication to attack

that does not also exist in the infected organism. Consequently, there are often side-effects to these drugs. Some of these side-effects can be life-threatening.

There are several classes of antifungal drugs.

Polyene antibiotic

The polyene antibiotics bind with sterols in the fungal cell wall, principally ergosterol. This causes the cell's contents to leak out and the cell dies. Animal cells contain cholesterol instead of ergosterol and so they are much less susceptible.

- Nystatin
Amphotericin B
Natamycin
Rimocidin
Filipin
Pimaricin

Imidazole and triazole

The imidazole and triazole groups of antifungal drugs inhibit the enzyme cytochrome P450 14±-demethylase. This enzyme converts lanosterol to ergosterol, and is required in fungal cell wall synthesis. These drugs also block steroid synthesis in humans.

Imidazoles:

- Miconazole
Ketoconazole
Clotrimazole
Econazole
Mebendazole
Bifonazole
Butoconazole
Fenticonazole
Isoconazole
Oxiconazole
Sertaconazole
Sulconazole
Thiabendazole
Tioconazole

The triazoles are newer, and are less toxic and more effective:

- Fluconazole
Itraconazole
Ravuconazole
Posaconazole
Voriconazole

Allylamines

Allylamines inhibit the enzyme squalene epoxidase, another enzyme required for ergosterol synthesis:

- Terbinafine - marketed as Lamisil in North America and the UK
Amorolfine
Naftifine
Butenafine

Echinocandin

Echinocandins inhibit the synthesis of glucan in the cell wall, probably via the enzyme 1,3-² glucan synthase:

- Anidulafungin
Caspofungin
Micafungin

Others

Others:

- Flucytosine is an antimetabolite.
Griseofulvin binds to polymerized microtubules and inhibits fungal mitosis.
Fluocinonide
Gentian Violet
Ciclopirox is a fungicidal
Tolnaftate is a fungicidal

Alternatives:

- Tea tree oil -- ISO 4730 ("Oil of Melaleuca, Terpinen-4-ol type")

Dandruff shampoos

Antifungal drugs are often found in dandruff shampoos. Among the most common are pyrithione zinc and selenium sulfide.

Garlic

Garlic plants

Scientific classification

Kingdom: Plantae

Division: Magnoliophyta

Class: Liliopsida

Order: Asparagales

Family: Alliaceae

Subfamily: Allioideae

Tribe: Allieae

Genus: Allium

***Species:* A. sativum**

Binomial name *Allium sativum*

Garlic (edible parts), Nutritional value per 100 g

Energy 150 kcal 620 kJ

Carbohydrates 33 g

Fat 0.5 g

Protein 6 g

Water 59 g

Vitamin B6 1.2 mg 92%

Percentages are relative to US RDI values for adults.
Source: ***USDA Nutrient database***

Garlic (Allium sativum) is a perennial plant in the family Alliaceae and genus Allium, closely related to the onion, shallot, and leek. It does not grow in the wild, and is thought to have arisen in cultivation, probably descended from the species Allium longicuspis, which grows wild in south-western Asia.[1] Garlic has been used throughout all of recorded history for both culinary and medicinal purposes.

The portion of the plant most often consumed is an underground storage structure called a *head*. A head of garlic is composed of a dozen or more discrete *cloves*, each of which is a botanical bulb, an underground structure comprised of thickened leaf bases. Each garlic clove may often be composed of just one leaf base, unlike onions, which almost always have multiple layers. The above-ground portions of the garlic plant are also sometimes consumed, particularly while immature and tender.

Garlic has a powerful pungent or "hot" flavor when raw, which mellows considerably when it is cooked. Raw or cooked, garlic is noted for its strong characteristic odor. [2]

Biology and chemistry

Because of its wide cultivation, the origins of garlic are not fully certain. It is related to onions and lilies, and cultivated in the same manner as the shallot. The domesticated garlic plant does not produce seeds, but is grown from bulbs. These bulbs are the part of the plant most commonly eaten, though some cooks also use the early spring shoots. These shoots are often pickled in Russia and states of the Caucasus and eaten as an appetizer. A common error made by novice cooks is to misinterpret the word "clove" as meaning the entire garlic head (naturally occurring cluster of cloves, depending on the species) rather than one of its segments, thereby wildly exaggerating the amount of garlic in a recipe.

A garlic head is generally four to eight centimeters in diameter, white to pinkish or purple, and is composed of numerous (8 - 25) discrete bulbs. The foliage comprises a central stem 25 - 100 cm tall, with flat or keeled (but not tubular) leaves 30 - 60 cm long and 2 - 3 cm broad. The flowers are produced in a small cluster at the top of the stem, often together with several bulblets, and surrounded by a papery basal spathe; each flower is white, pink or purple, with six tepals 3 - 5 millimetres long. The flowers are commonly abortive and rarely produce any seeds.

The garlic plant has long, narrow, flat, obscurely keeled leaves. The head (compound bulb) has a flaky, mostly white outer layers of skin like that of an onion. Inside are 8-25 cloves, or smaller bulbs. From these, new bulbs can be procured by planting out in late winter or early spring.

The percentage composition of the bulbs is given by E. Solly (Trans. Hon. Soc. Loud., new ser., iii. p. 60) as water 84.09 %, organic matter 13.38 %, and inorganic matter 1.53 % - that of the leaves being water 87.14 %, organic matter 11.27 % and inorganic matter 1.59 %.

Like other members of the onion family, garlic actually creates the chemicals that give it its sharp flavor when the plant's cells are damaged. When a cell of a garlic clove is broken by chopping, chewing, or crushing, enzymes stored in cell vacuoles trigger the breakdown of several sulfur-containing compounds stored in the cell fluids. The resultant compounds are

responsible for the sharp or hot taste and strong smell of garlic. Some of the compounds are unstable and continue to evolve over time. Among the members of the onion family, garlic has by far the highest concentrations of initial reaction products, making garlic much more potent than onions, shallots, or leeks.[3] Although people have come to enjoy the taste of garlic, these compounds are believed to have evolved as a defensive mechanism, deterring animals like birds, insects, and worms from eating the plant.[4]

A large number of sulfur compounds contribute to the smell and taste of garlic. Diallyl disulfide is believed to be an important odor component. Allicin has been found to be the compound most responsible for the spiciness of raw garlic. This chemical opens thermoTRP (transient receptor potential) channels that are responsible for the burning sense of heat in foods. The process of cooking garlic removes allicin, thus mellowing its spiciness.[5]

Uses

Culinary use

Garlic is most often used as a seasoning or a condiment. When crushed or finely chopped it yields allicin, a powerful antibiotic and anti-fungal compound (phytoncide). It also contains alliin, ajoene, enzymes, vitamin B, minerals, and flavonoids.

Garlic is widely used in many forms of cooking for its strong flavor, which is considered to enhance many other flavors. Depending on the form of cooking and the desired result, the flavor is either mellow or intense. It is often paired with onion, tomato, and/or ginger.

In culinary preparation, it is necessary to remove the parchment-like skin from individual cloves before chopping. Lightly crushing the cloves with the ball of the hand or flat of a knife makes this job much easier. Neither garlic nor herbs should be stored while covered in cooking oil as it is possible for botulism organisms to grow in the oxygen-free oil.

When eaten in quantity, garlic may be strongly evident in the diner's sweat and breath the following day. This is because garlic's strong smelling sulfur compounds are metabolized forming allyl methyl sulfide. Allyl methyl sulfide (AMS) cannot be digested and is passed into the blood. It is carried to the lungs and the skin where it is excreted. Since digestion takes several hours, and release of AMS several hours more, the effect of eating garlic may be present for a long time.

The well-known phenomenon of "garlic breath" is alleged to be alleviated by eating fresh parsley. This is, therefore, included in many garlic recipes, e.g. Pistou and Persillade. However, since garlic breath results mainly from digestive processes placing compounds such as AMS in the blood, and AMS is then released through the lungs over the course of many hours, eating parsley is at best a temporary fix. One way of accelerating the release of AMS from the body is the use of a sauna. Because of its strong odor, garlic is sometimes called the "stinking rose".

Hardneck garlic varieties feature a seedpod that grows atop a leafless stalk known as a "scape". Immature scapes are tender and edible. They are also known as "garlic spears", "stems", or "tops". Scapes generally have a milder taste than cloves. They are often used in stir frying or prepared like asparagus.

Medicinal use

Components of garlic

Phytochemicals

Allicin

Beta-carotene

Beta-sitosterol

Caffeic acid

Chlorogenic acid

Diallyl disulfide

Ferulic acid

Geraniol

Kaempferol

Linalool

Oleanolic acid

P-coumaric acid

Phloroglucinol

Phytic acid

Quercetin

Rutin

S-Allyl cysteine

Saponin

Sinapic acid

Stigmasterol
Alliin

Nutrients

Calcium

Folate

Iron

Magnesium

Manganese

Phosphorus

Potassium

Selenium

Zinc

Vitamin B1 (Thiamine)

Vitamin B2 (Riboflavin)

Vitamin B3 (Niacin)
Vitamin C

Source: Balch p 97[6]

Some scientific research indicates that garlic can have some health benefits, such as preventing and fighting common cold[7],diminishment of platelet aggregation[8]; a meta-analysis showing significant (8% compared to placebo) lowering of Low density lipoprotein carrying cholesterol (LDL-C) [9]; treatment of hyperlipidaemia[10]; the significant inhibition of atherosclerosis via the use of aged garlic extract Kyolic[11]; and the protective nature of chronic garlic intake on elastic properties of aorta in the elderly[12]. Regular and prolonged use of therapeutic amounts of aged garlic extracts lower blood homocysteine levels, and prevent some complications of diabetes mellitus. It may have some cancer-fighting properties because it is high in diallyl sulphide (DADs), believed to be an anticarcinogen.[13]

In modern naturopathy, garlic is used as a treatment for intestinal worms, both orally and as an anal suppository.

Garlic cloves continue to be used by aficionados as a remedy for infections (especially chest problems), digestive disorders, and fungal infections such as thrush. They are claimed to be an effective long-term remedy for cardiovascular problems reducing excessive blood cholesterol levels, atherosclerosis, the risk of thrombosis, and hypertension but these claims are disputed, as there has been no clinical trial that has demonstrated any such benefits. Whole cloves used as vaginal suppositories are sometimes used as a home remedy for Candidiasis (yeast infections). Garlic is also alleged to help regulate blood sugar levels, and

so can be helpful in late-onset diabetes, though people taking insulin should not consume medicinal amounts of garlic without consulting a physician. In such applications, garlic must be fresh and uncooked, or the allicin will be lost.

Dietary supplements in pill form, as are commonly available, claim to possess the medicinal benefits of garlic, without (in the words of one manufacturer) "the unsocial qualities associated with fresh garlic cloves".

History

From the earliest times garlic has been used as an article of diet. It is very widely used in Lebanese cuisine. Many Lebanese salads contain a garlic sauce. It formed part of the food of the Israelites in Egypt (Numb. xi. 5) and of the labourers employed by Khufu in constructing the pyramid. Garlic is still grown in Egypt, but the Syrian variety is the kind most esteemed now (see Rawlinson's Herodotus, 2.125).

It was consumed by the ancient Greek and Roman soldiers, sailors and rural classes (cf. Virg. Ed. ii. II), and, as Pliny tells us (N.H. xix. 32), by the African peasantry. Galen eulogizes it as the "rustic's theriac" (cure-all) (see F Adams's Paulus Aegineta, p. 99), and Alexander Neckam, a writer of the 12th century (see Wright's edition of his works, p. 473, 1863), recommends it as a palliative of the heat of the sun in field labor.

Pliny the Elder, in his Natural History, (N.H. xx. 23) gives an exceedingly long list of scenarios in which it was considered beneficial. Dr. T. Sydenham valued it as an application in confluent smallpox, and, says Cullen (Mat. Med. ii. p. 174, 1789), found some dropsies cured by it alone. Early in the 20th century, it was sometimes used in the treatment of pulmonary tuberculosis or phthisis.

Garlic was rare in traditional English cuisine (though it is said to have been grown in England before 1548), and has been a much more common ingredient in Mediterranean Europe. Garlic was placed by the ancient Greeks on the piles of stones at cross-roads, as a supper for Hecate (Theophrastus, Characters, The Superstitious Man); and according to Pliny, garlic and onions were invoked as deities by the Egyptians at the taking of oaths. The inhabitants of Pelusium in lower Egypt, who worshipped the onion, are said to have had an aversion to both onions and garlic as food.

To prevent the plant from running to leaf, Pliny (Nat. Hist. xix. 34) advised bending the stalk downward and covering with earth; seeding, he observes, may be prevented by twisting the stalk (by "seeding", he most likely means the development of small, less potent bulbs).

Superstition and mythology

Garlic has been seen as a force for both good and evil. A Christian myth says that after Satan left the Garden of Eden, garlic arose in his left footprint, and onion in the right.[14] Even in Europe, though, many cultures have turned to garlic as a protective force or white magic, perhaps because of its reputation as a powerful preventative medicine.[15] Central European folk beliefs considered garlic a powerful ward against devils, werewolves, and

vampires.[15] To ward off vampires, garlic could be worn on one's person, hung in windows, or rubbed on chimneys and keyholes.[16]

Classification

Classification of culinary garlic can be complex, with numerous cultivars being grown. The broadest division is into "hardneck" and "softneck" types; very broadly speaking, hardnecks have more intense flavours (which are more closely related to their wild ancestor) but lesser storage capabilities, while conversely softnecks are excellent "keepers" but often milder (those are broad-brush simplifications with numerous exceptions and half-exceptions). Within those two types, there are usually felt to be three subdivisions of hardnecks and two of softnecks.

The "wild garlic", "crow garlic" and "field garlic" of Britain are the species Allium ursinum, A. vineale and A. oleraceum, respectively. In North America, "wild garlic" or "crow garlic" is Allium vineale, and along with "wild onion" (also known as "meadow garlic" or "wild garlic") Allium canadensis, are common weeds in fields. Elephant garlic is a variant of the leek species, A. ampeloprasum, and is larger and milder than true garlic.[17]

Preservation

The types differ not only in culinary qualities, but in storage potential. Under good storage conditions, which are not hard to achieve (room temperature and medium to low humidity), one can hope for these results:

- Asiatic, Turban and Porcelain types: a few months
- Rocambole and Purple Stripe types: 6 to 8 months
- Artichoke types: 8 to 10 months
- Silverskin (including Creole) types: up to a full year

Rocamboles, however, have a tendency to dehydrate in storage under dry conditions (less than about 50% humidity).

The bulbs are best preserved hung in a dry place. If of fair size, four to six of them weigh about 500 g (1 lb). Also, it is very important to keep them out of the sun. A dark corner of the room is best.

Do not store garlic in oil at room temperature. See *Caution*, below.

Caution

- Cases of botulism have been caused by consuming garlic-in-oil preparations. It is important to add acid when creating these mixtures and to keep them refrigerated to retard bacterial growth. [18]
- While culinary quantities are generally safe, during pregnancy and lactation garlic can cause digestive problems such as heartburn, and babies may dislike the taste in breast milk.
- The medicinal effects of taking garlic long-term are largely unknown, and no FDA approved study has been performed.

Trivia

- South Korea is the largest consumer of garlic.
- In the United States, Gilroy, California promotes itself as "Garlic Capital of the World", and hosts the Gilroy Garlic Festival every summer.
- In 2005, a poll of 2,000 people revealed garlic to be Britain's 6th favourite culinary vegetable. [1]
- In the televised cartoon shorts, before he used spinach as a source of superhuman strength, comic book character Popeye's ancestor Hercules would sniff fresh bulbs of unpeeled garlic.
- Garlic is Wario's favorite food. When he eats it in WarioWare: Touched!, he becomes Wario-Man.

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Notes

1. ^ Saulnkhe and Kadam p. 397
2. ^ Gernot Katzer's Spice Pages.
3. ^ McGee p. 310-311
4. ^ Macpherson et al. section "Conclusion"
5. ^ Macpherson et al.
6. ^ Balch, Phyllis A. (2000). Prescription for Nutritional Healing, 3rd ed. New York: Avery. p. 97.
7. ^ http://news.bbc.co.uk/2/hi/health/1575505.stm
8. ^ http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=9641475&dopt=Citation
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10. ^ http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=2291748&dopt=Abstract

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12. ^ http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=9355906&dopt=Citation

13. ^ Abstract

14. ^ Pickering, David (2003). Cassell's Dictionary of Superstitions. Sterling Publishing. ISBN 0-304-36561-0. p. 211
15. ^ **a** b McNally, Raymond T (1994). In Search of Dracula. Houghton Mifflin. ISBN 0-395-65783-0. p. 120.
16. ^ McNalley p. 122; Pickering p. 211.
17. ^ McGee p. 112

18. ^ http://www.colostate.edu/Orgs/safefood/NEWSLTR/v2n4s08.html

Antiparasitic agents

Antiparasitics are a class of medications which are indicated for the treatment of infection by parasites such as nematodess, cestodes, trematodes, infectious protozoa, and amoebas.

Antinematodes

- Mebendazole (for most nematode infections)

Pyrantel pamoate (for most nematode infections)
Thiabendazole (for roundworm infections)
Diethycarbazine (for treatment of Lymphatic filariasis)

Anticestodes

- Niclosamide (for tapeworm infections)

Parziquantel (for tapeworm infections)

Antitrematodes

- Parziquantel

Antiamoebics

- Rifampin
Amphotericin B

Antiprotozoals

- Melarsoprol (for treatment of sleeping sickness caused by Trypanosoma brucei)

Anthelmintics

Anthelmintics (in the U.S., *antihelminthics*) are drugs that expel parasitic worms (helminths) from the body, by either killing or stunning them. A traditional remedy of this type is often called a *vermifuge*.

Examples of drugs used as anthelmintics include:

- Albendazole - Effective against: threadworms, roundworms, whipworms, tapeworms, hookworms
Diethylcarbamazine - Effective against: Wuchereria bancrofti, Brugia malayi, Brugia timori, tropical pulmonary eosinophilia, loiasis
Mebendazole - Effective against: pinworms, roundworms and hookworms
Niclosamide - Effective against: tapeworms
Ivermectin - Effective against: most common intestinal worms (except tapeworms)
Suramin
Thiabendazole - Effective against: roundworms, hookworms

According to the United States Army Field Manual, there are several other common products which can be used (albeit dangerously) as antihelmintics:

- Saltwater. Mix 4 tablespoons of salt (NaCl) in 1 quart of water and drink. Never repeat this treatment.
- Tobacco - Eat 1 to 1.5 cigarettes. The nicotine in the tobacco will kill or stun the worms long enough for you to expel them.
- Kerosene - At the most, drink 2 tablespoons of kerosene. If necessary, you can repeat this in several days (1 to 2 days at the least).
- Hot peppers - Peppers are effective only when they are a steady part of your diet. You can eat them raw or add them to food.

Many members of the piperazine family are successful anthelmintics.

Natural anthelmintics include black walnut, wormwood (Artemisia absynthium), clove (Syzygium aromaticum), tansy tea (Tanacetum vulgare), Hagenia (Hagenia abyssinica), and the male fern (Dryopteris filix-mas).

The macroinvertebrate parasites treated in this way include, for instance, tapeworms and roundworms, which infest the intestines.

References

1. US Army Survival Manual (reprint of Department of the Army Field Manual, FM 21-76). Platnum Press (2004). ISBN 0-7607-4988-4

Antiprotozoal agent

Antiprotozoal agents (ATC code: ATC P01) is a class of pharmaceuticals used in treatment of protozoal infections.

Examples:

- Eflornithine

Furazolidone
Melarsoprol
Metronidazole
Ornidazole
Paromomycin sulfate
Pentamidine
Pyrimethamine
Tinidazole

Antimalarial agents

Antimalarial drugs are designed to prevent or treat malaria. There are many of these drugs currently on the market. Here is a partial list.

Antimalarial drugs currently used for treatment

- mefloquine (Lariam ®)

chloroquine
fansidar (pyrimethamine, sulfadoxine)
amodiaquine

- quinine/quinidine
- artemisinin/artemether/artesunate

atovaquone
lumefatrine

Antimalarial drugs currently used for prophylaxis

- mefloquine
  chloroquine
  proguanil
  pyrimethamine (daraprim)
- doxycycline
  - hydroxychloroquine (Plaquenil)

Antiseptics

Antiseptics (Greek ±½Ä¹, against, and Ã·ÀÄ¹º¿Â, putrefactive) are antimicrobial substances that are applied to living tissue/skin to to reduce the possibility of infection, sepsis, or putrefaction. They should generally be distinguished from antibiotics that destroy microorganisms within the body, and from disinfectants, which destroy microorganisms found on non-living objects. Some antiseptics are true germicides, capable of destroying microbes (bacteriocidal), whilst others are bacteriostatic and only prevent or inhibit their growth. Antibacterials are antiseptics that only act against bacteria.

Use in surgery

The widespread introduction of antiseptic surgical methods followed the publishing of the paper Antiseptic Principle of the Practice of Surgery in 1867 by Joseph Lister, inspired by Louis Pasteur's germ theory of putrefaction. In this paper he advocated the use of carbolic acid (phenol) as a method of ensuring that any germs present were killed. Some of this work was preceded slightly by that of Dr. George H Tichenor and Ignaz Semmelweis.

But every antiseptic, however good, is more or less toxic and irritating to a wounded surface. Hence it is that the antiseptic method has been replaced in the surgery of today by the aseptic method, which relies on keeping free from the invasion of bacteria rather than destroying them when present.

How it works

For the growth of bacteria there must be a certain food supply, moisture, in most cases oxygen, and a certain minimum temperature (see bacteriology). These conditions have been specially studied and applied in connection with the preserving of food and in the ancient practice of embalming the dead, which is the earliest illustration of the systematic use of antiseptics.

In early inquiries a great point was made of the prevention of putrefaction, and work was done in the way of finding how much of an agent must be added to a given solution, in order that the bacteria accidentally present might not develop. But for various reasons this was an inexact method, and to-day an antiseptic is judged by its effects on pure cultures of definite pathogenic microbes, and on their vegetative and spore forms. Their standardization has

been effected in many instances, and a water solution of phenol of a certain fixed strength is now taken as the standard with which other antiseptics are compared.

Some common antiseptics

Alcohols Most commonly used are ethanol (60-90%), 1-propanol (60-70%) and 2-propanol/isopropanol (70-80%) or mixtures of these alcohols. They are commonly reffered to as "surgical alcohol". Used to disinfect the skin before injections are given, often along with iodine (tincture of iodine) or some cationic surfactants (benzalkonium chloride 0.05 - 0.5%, chlorhexidine 0.2 - 4.0% or octenidine dihydrochloride 0.1 - 2.0%).

Quaternary ammonium compounds Also known as Quats or QAC's, include the chemicals benzalkonium chloride (BAC), cetyl trimethylammonium bromide (CTMB), cetylpyridinium chloride (Cetrim), cetylpyridinium chloride (CPC) and benzethonium chloride (BZT). Benzalkonium chloride is used in some pre-operative skin disinfectants (conc. 0.05 - 0.5%) and antiseptic towels. The antimicrobial activity of Quats is inactivated by anionic surfactants, such as soaps. Related disinfectants include chlorhexidine and octenidine.

Boric acid Used in suppositories to treat yeast infections of the vagina, in eyewashes, and as an antiviral to shorten the duration of cold sore attacks. Put into creams for burns. Also common in trace amounts in eye contact solution. Though it is popularly known as an antiseptic, it is in reality only a soothing fluid, and bacteria will flourish comfortably in contact with it.

Chlorhexidine Gluconate A biguanidine derivative, used in concentrations of 0.5 - 4.0% alone or in lower concentrations in combination with other compounds, such as alcohols. Used as a skin antiseptic and to treat inflammation of the gums (gingivitis). The microbicidal action is somewhat slow, but remanent. It is a cationic surfactant, similar to Quats.

Hydrogen peroxide Used as a 6% (20Vols) solution to clean and deodorise wounds and ulcers. More common 1% or 2% solutions of hydrogen peroxide have been used in household first aid for scrapes, etc. However, even this less potent form is no longer recommended for typical wound care as the strong oxidization causes scar formation and increases healing time. Gentle washing with mild soap and water or rinsing a scrape with sterile saline is a better practice.

Iodine Usually used in an alcoholic solution (called tincture of iodine) or as Lugol's iodine solution as a pre- and post-operative antiseptic. No longer recommended to disinfect minor wounds because it induces scar tissue formation and increases healing time. Gentle washing with mild soap and water or rinsing a scrape with sterile saline is a better practice. Novel iodine antiseptics containing iodopovidone/PVP-I (an iodophor, complex of povidone, a water-soluble polymer, with triiodide anions I3-, containing about 10% of active iodine, with the commercial name Betadine) are far better tolerated, don't affect wound healing negativelly and leave a depot of active iodine, creating the so-called "remanent," or persistent, effect. The great advantage of iodine antiseptics is the widest scope of antimicrobial activity, killing all principial pathogenes and given enough time even spores, which are considered to be the most difficult form of microorganisms to be inactivated by disinfectants and antiseptics.

Mercurochrome Not recognized as safe and effective by the U.S. Food and Drug Administration (FDA) due to concerns about its mercury content. Another obsolete organomercury antiseptics include bis-(fenylmercury) monohydrogenborate (Famosept).

Octenidine dihydrochloride A cationic surfactant and bis-(dihydropyridinyl)-decane derivative, used in concentrations of 0.1 - 2.0%. It is similar in its action to the Quats, but is of somewhat broader spectrum of activity. Octenidine is currently increasingly used in continental Europe as a QAC's and chlorhexidine (with respect to its slow action and concerns about the carcinogenic impurity 4-chloroaniline) substitute in water- or alcohol-based skin, mucosa and wound antiseptic. In aqueous formulations, it is often potentiated with addition of 2-phenoxyethanol.

Phenol (carbolic acid) compounds Phenol is germicidal in strong solution, inhibitory in weaker ones. Used as a "scrub" for pre-operative hand cleansing. Used in the form of a powder as an antiseptic baby powder, where it is dusted onto the belly button as it heals. Also used in mouthwashes and throat lozenges, where it has a methadone-like painkilling effect as well as an antiseptic one. Example: TCP. Other phenolic antiseptics include historically important, but today rarely used (sometimes in dental surgery) thymol, today obsolete hexachlorophene, still used triclosan and sodium 3,5-dibromo-4-hydroxybenzenesulfonate (Dibromol).

Sodium chloride Used as a general cleanser. Also used as an antiseptic mouthwash. Only a weak antiseptic effect, due to hyperosmolality of the solution above 0.9%.

Sodium hypochlorite Used in the past, diluted, neutralised and combined with potassium permanganate in the Daquin's solution. Nowadays used only as disinfectant.

See also

- Disinfection

References

- This article incorporates text from the Encyclopædia Britannica Eleventh Edition, a publication now in the public domain.

Iodine

Name, Symbol, Number: iodine, I, 53

Chemical series halogens

Group, Period, Block: 17, 5, p

Appearance violet-dark gray, lustrous

Atomic mass 126.90447(3) g/mol

Electron configuration [Kr] 4d10 5s2 5p5

Electrons per shell 2, 8, 18, 18, 7

Physical properties

phase solid

Density (near r.t.) 4.933 g·cm3

Melting point 386.85 K (113.7 °C, 236.66 °F)

Boiling point 457.4 K (184.3 °C, 363.7 °F)

Critical point 819 K, 11.7 MPa

Heat of fusion (I*2*) 15.52 kJ·mol1

Heat of vaporization (I*2*) 41.57 kJ·mol1

Heat capacity (25 °C) (I*2*) 54.44 J·mol1·K1

Vapor pressure (rhombic)

P/Pa	1	10	100	1 k	10 k	100 k
at T/K	260	282	309	342	381	457

Atomic properties

Crystal structure orthorhombic

Oxidation states ±1, 5, 7 (strongly acidic oxide)

Electronegativity 2.66 (Pauling scale)

Ionization energies 1st: 1008.4 kJ/mol, 2nd: 1845.9 kJ/mol, 3rd: 3180 kJ/mol

Atomic radius 140 pm

Atomic radius (calc.) 115 pm

Covalent radius 133 pm

Van der Waals radius 198 pm

Miscellaneous

Magnetic ordering nonmagnetic

Electrical resistivity (0 °C) 1.3×107 ©·m

Thermal conductivity (300 K) 0.449 W·m1·K1

Bulk modulus 7.7 GPa

CAS registry number 7553-56-2

Selected isotopes

Main article: Isotopes of iodine

iso	NA	half-life	DM	DE (MeV)	DP
^{127}I	100%	I is stable with 74 neutrons			
^{129}I	syn	1.57×10^{7} y	$Beta^{-}$	0.194	^{129}Xe
^{131}I	syn	8.02070 d	$Beta^{-}$	0.971	^{131}Xe

References

Iodine (IPA: /ÈŒjY(Š)ÌdiÐn/, Greek: iodes, meaning "violet"), is a chemical element in the periodic table that has the symbol I and atomic number 53. Chemically, iodine is the least reactive of the halogens, and the most electropositive halogen after astatine. Iodine is primarily used in medicine, photography and dyes. It is required in trace amounts by most living organisms.

As with all other halogens (members of Group VII in the Periodic Table), iodine forms diatomic molecules, and hence, has the molecular formula of $I2$.

Occurrence on earth

Iodine naturally occurs in the environment chiefly as dissolved iodide in seawater, although it is also found in some minerals and soils. The element may be prepared in an ultrapure form through the reaction of potassium iodide with copper(II) sulfate. There are also several other methods of isolating this element. Although the element is actually quite rare, kelp and certain other plants have the ability to concentrate iodine, which helps introduce the element into the food chain as well as keeping its cost down.

Uses

Iodine is used in pharmaceuticals, antiseptics, medicine, food supplements, dyes, catalysts and photography.

Isotopes

There are 37 isotopes of iodine and only one, 127I, is stable.

In many ways, 129I is similar to 36Cl. It is a soluble halogen, fairly non-reactive, exists mainly as a non-sorbing anion, and is produced by cosmogenic, thermonuclear, and in-situ reactions. In hydrologic studies, 129I concentrations are usually reported as the ratio of 129I to total I (which is virtually all 127I). As is the case with 36Cl/Cl, 129I/I ratios in nature are quite small, 1014 to 1010 (peak thermonuclear 129I/I during the 1960s and 1970s reached about 107). 129I differs from 36Cl in that its half-life is longer (15.7 vs. 0.301 million years), it is highly biophilic, and occurs in multiple ionic forms (commonly, I and IO3) which have different chemical behaviors. This makes it fairly easy for 129I to enter the biosphere as it becomes incorporated into vegetation, soil, milk, animal tissue, etc.

Excesses of stable 129Xe in meteorites have been shown to result from decay of "primordial" 129I produced newly by the supernovas which created the dust and gas from which the solar system formed. 129I was the first extinct radionuclide to be identified as present in the early solar system. Its decay is the basis of the I-Xe radiometric dating scheme, which covers the first 50 million years of solar system evolution.

Effects of various radioiodine isotopes in biology are discussed below.

Notable characteristics

Iodine is a dark-gray/purple-black solid that sublimes at standard temperatures into a purple-pink gas that has an irritating odor. This halogen forms compounds with many elements, but is less active than the other members of its Group VII (halogens) and has some metallic-like properties. Iodine dissolves easily in chloroform, carbon tetrachloride, or carbon disulphide to form purple solutions (It is only slightly soluble in water, giving a yellow solution). The deep blue color of starch-iodine complexes is produced only by the free element.

Many students who have seen the classroom demonstration where iodine crystals are gently heated in a test tube come away with the impression that liquid iodine cannot exist at atmospheric pressure. This misconception arises because sublimation occurs without the intermediacy of liquid. The truth is that if iodine crystals are heated carefully to their melting point of 113.7 °C, the crystals will fuse into a liquid, which will be present under a dense blanket of the vapour.

Descriptive Chemistry

Elemental iodine is poorly soluble in water, with one gram dissolving in 3450 ml at 20 °C and 1280 ml at 50 °C. By contrast with chlorine, the formation of the hypohalite ion (IO–) in neutral aqueous solutions of iodine is negligible.

I*2*+ H*2*0 Ë H+ + I– + HIO (K = 2.0×10-13) [1]

Solubility in water is greatly improved if the solution contains dissolved iodides such as hydroiodic acid, potassium iodide, or sodium iodide. Dissolved bromides also improve water solubility of iodine. Iodine is soluble in a number of organic solvents, including ethanol (20.5 g/100 ml at 15 °C, 21.43 g/100 ml at 25 °C), diethyl ether (20.6 g/100 ml at 17 °C, 25.20

g/100 ml at 25 °C), chloroform, acetic acid, glycerol, benzene (14.09 g/100 ml at 25 °C), carbon tetrachloride (2.603 g/100 ml at 35 °C), and carbon disulfide (16.47 g/100 ml at 25 °C)[2]. Aqueous and ethanol solutions are brown. Solutions in chloroform, carbon tetrachloride, and carbon disulfide are violet.

Elemental iodine can be prepared by oxidizing iodides with chlorine:

$2I^- + Cl_2 \rightarrow I_2 + 2Cl^-$

or with manganese dioxide in acid solution:[1]

$2I^- + 4H^+ + MnO_2 \rightarrow I_2 + 2H_2O + Mn^{++}$

Iodine is reduced to hydroiodic acid by hydrogen sulfide:[3]

$I_2 + H_2S \rightarrow 2HI + S\downarrow$

or by hydrazine:

$2I_2 + N_2H_4 \rightarrow 4HI + N_2$

Iodine is oxidized to iodate by nitric acid:[4]

$I_2 + 10HNO_3 \rightarrow 2HIO_3 + 10NO_2 + 4H_2O$

or by chlorates:[4]

$I_2 + 2ClO_3^- \rightarrow 2IO_3^- + Cl_2$

Iodine is converted in a two stage reaction to iodide and iodate in solutions of alkali hydroxides (such as sodium hydroxide):[1]

$I_2 + 2OH^- \rightarrow I^- + IO^- + H_2O$ K = 30)

$3IO^- \rightarrow 2I^- + IO_3^-$ (K = 10^{20})

History

Iodine was discovered by Bernard Courtois in 1811. He was born to a manufacturer of saltpeter (potassium nitrate, a vital part of gunpowder). At the time France was at war, saltpeter, a component of gunpowder, was in great demand. Saltpeter produced from French niter beds required sodium carbonate, which could be isolated from seaweed washed up on the coasts of Normandy and Brittany. To isolate the sodium carbonate, seaweed was burned and the ash then washed with water. The remaining waste was destroyed by adding sulfuric acid. One day Courtois added too much sulfuric acid and a cloud of purple vapor rose. Courtois noted that the vapor crystallized on cold surfaces making dark crystals. Courtois suspected that this was a new element but lacked the money to pursue his observations.

However he gave samples to his friends, Charles Bernard Desormes (1777 - 1862) and Nicolas Clément (1779 - 1841) to continue research. He also gave some of the substance to Joseph Louis Gay-Lussac (1778 - 1850), a well-known chemist at that time, and to André-Marie Ampère (1775 - 1836). On 29 November 1813 Dersormes and Clément made public Courtois' discovery. They described the substance to a meeting of the Imperial Institute of France. On December 6 Gay-Lussac announced that the new substance was either an element or a compound of oxygen. Ampère had given some of his sample to Humphry Davy (1778 - 1829). Davy did some experiments on the substance and noted its similarity to chlorine. Davy sent a letter dated December 10 to the Royal Society of London stating that he had identified a new element. A large argument erupted between Davy and Gay-Lussac over who identified iodine first but both scientists acknowledged Barnard Courtois as the first to isolate the chemical element.

Notable inorganic iodine compounds

- Ammonium iodide (NH4I)

Caesium iodide (CsI)
Copper(I) iodide (CuI)
Hydroiodic acid (HI)
Iodic acid (HIO3)
Iodine cyanide (ICN)
Iodine heptafluoride (IF7)
Iodine pentafluoride (IF5)
Lead(II) iodide (PbI2)
Lithium iodide (LiI)
Nitrogen triiodide (NI3)
Potassium iodide (KI)

- Sodium iodide (NaI)

Stable iodine in biology

One of the halogens, iodine is an essential trace element; the thyroid hormones, thyroxine and triiodothyronine contain iodine.

Iodine has a single known role in biology: it is an essential trace element since the thyroid hormones, thyroxine (T4) and triiodothyronine (T3) contain iodine. These are made from addition condensation products of the amino acid tyrosine, and are stored prior to release in a protein-like molecule called thryroglobulin. T4 and T3 contain four and three atoms of iodine per molecule, respectively. The thyroid gland actively absorbs iodide ion from the blood to make and release these hormones into the blood, actions which are regulated by a second hormone TSH from the pituitary. Thyroid hormones are phylogenetically very old molecules which are sythesized by most multicellular organisms, and which even have some effect on unicellular organisms.

Thyroid hormones play a very basic role in biology, acting on gene transcription to regulate the basal metabolic rate. The total deficiency of thyroid hormones can reduce basal metabolic rate up to 50%, while in excessive production of thyroid hormones the basal

metabolic rate can be increased by 100%. T4 acts largely as a precursor to T3, which is (with some minor exceptions) the biologically active hormone.

Dietary intake

The United States Food and Drug Administration recommends (21 CFR 101.9 (c)(8)(iv)) 150 micrograms of iodine per day for both men and women. This is necessary for proper production of thyroid hormone. Natural sources of iodine include seaweed, such as kelp and seafood. [1] Salt for human consumption is often enriched with iodine and is referred to as iodized salt.

Iodine deficiency

In areas where there is little iodine in the diet—typically remote inland areas and semi-arid equatorial climates where no marine foods are eaten—iodine deficiency gives rise to goiter, so called endemic goiter. The mechanism is that low amounts of thyroid hormone in the blood due to lack of iodine to make them, give rise to high levels of the pituitary hormone TSH, which in turn stimulates abnormal growth of the thyroid gland. In some such areas, this is now combatted by the addition of small amounts of iodine to table salt in form of sodium iodide, potassium iodide, potassium iodate—this product is known as iodized salt. Iodine compounds have also been added to other foodstuffs, such as flour, in areas of deficiency.

Iodine deficiency is the leading cause of preventable mental retardation, an effect which happens primarily when babies and small children are made hypothyroid by lack of the element (this condition in adults results in mental slowing, but by itself, almost never causes severe or irreversible mental problems). Iodine deficiency remains a serious public health problem in developing countries.

Toxicity of Iodine

Excess iodine has symptoms similar to those of iodine deficiency. Commonly encountered symptoms are abnormal growth of the thyroid gland and disorders in functioning and growth of the organism as a whole.

Elemental iodine, I_2, is deadly poison if taken in larger amounts; if 2-3 grams of it is consumed, it is fatal to humans.

Iodides are similar in toxicity to bromides.

Radioiodine and biology

Radioiodine and the thyroid

The artificial radioisotope 131I (a beta emitter), also known as radioiodine which has a half-life of 8.0207 days, has been used in treating cancer and other pathologies of the thyroid glands. 123I is the radioisotope most often used in nuclear imaging of the kidney and thyroid as well as thyroid uptake scans (used for the evaluation of Grave's disease). The most

common compounds of iodine are the iodides of sodium and potassium (KI) and the iodates (KIO_3).

129I (half-life 15.7 million years) is a product of 130Xe spallation in the atmosphere and uranium and plutonium fission, both in subsurface rocks and nuclear reactors. Nuclear processes, in particular nuclear fuel reprocessing and atmospheric nuclear weapons tests have now swamped the natural signal for this isotope. 129I was used in rainwater studies following the Chernobyl accident. It also has been used as a ground-water tracer and as an indicator of nuclear waste dispersion into the natural environment.

If humans are exposed to radioactive iodine, the thyroid gland will absorb it as if it were non-radioactive iodine, leading to elevated chances of thyroid cancer. Isotopes with shorter half-lifes such as **131**I present a greater risk than those with longer half-lives since they generate more radiation per unit of time. Taking large amounts of regular iodine will saturate the thyroid and prevent uptake. Iodine pills are sometimes distributed to persons living close to nuclear establishments, for use in case of accidents that could lead to releases of radioactive iodine.

- Iodine-123 and iodine-125 are used in medicine as tracers for imaging and evaluating the function of the thyroid.
- Iodine-131 is used in medicine for treatment of thyroid cancer and Grave's disease.
- Uncombined (elemental) iodine is mildly toxic to all living things.
- Potassium iodide (KI tablets, or "SSKI" = "Super-Saturated KI" liquid drops) can be given to people in a nuclear disaster area when fission has taken place, to flush out the radioactive iodine-131 fission product. The half-life of iodine-131 is only eight days, so the treatment would need to continue only a couple of weeks. In cases of leakage of certain nuclear materials without fission, or certain types of dirty bomb made with other than radioiodine, this precaution would be of no avail.

Radioiodine and the kidney

In the 1970s imaging techniques were developed in California to utilize radioiodine in diagnostics for renal hypertension.

Non-hormone-related applications of iodine

- Tincture of iodine (3% elemental iodine in water/ethanol base) is an essential component of any emergency survival kit, used both to disinfect wounds and to sanitize surface water for drinking (3 drops per liter, let stand for 30 minutes). Alcohol-free iodine solutions such as Lugol's iodine, as well as other free iodine-providing antiseptics iodophors, are also available as effective elemental iodine sources for this purpose.
- Iodine compounds are important in the field of organic chemistry and are very useful in medicine.
- Silver iodide is used in photography.

- Tungsten iodide is used to stabilize the filaments in light bulbs.
- Nitrogen triiodide is an explosive, too unstable to be used commercially, but is commonly used in college pranks.

Precautions for stable iodine

Direct contact with skin can cause lesions, so it should be handled with care. Iodine vapor is very irritating to the eye and to mucous membranes. Concentration of iodine in the air should not exceed 1 mg/m^3 (eight-hour time-weighted average). When mixed with ammonia, it can form nitrogen triiodide which is extremely sensitive and can explode unexpectedly.

Clandestine Use

In the United States, the Drug Enforcement Agency (DEA) regards iodine and compounds containing iodine (ionic iodides, iodoform, ethyl iodide, and so on) as reagents useful for the clandestine manufacture of methamphetamine. Persons who attempt to purchase significant quantities of such chemicals without establishing a legitimate use are likely to find themselves the target of a DEA investigation. Persons selling such compounds without doing due diligence to establish that the materials are not being diverted to clandestine use may be subject to stiff fines [5][6]

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1. ^ ***a*** ***b*** ***c*** Advanced Inorganic Chemistry by Cotton and Wilkinson, 2nd ed.
2. ^ Merck Index of Chemicals and Drugs, 9th ed.
3. ^ General Chemistry (volume 2) by N.L. Glinka, Mir Publishing 1981
4. ^ ***a*** ***b*** General Chemistry by Linus Pauling, 1947 ed.
5. ^ 21 USC Sec. 872 01/22/02
6. ^ Chemical Supplier Convicted of Diversion of Iodine

- Los Alamos National Laboratory - Iodine
- 21 CFR 101.9 (c)(8)(iv) (Text PDF) — FDA nutritional facts label information for vitamins and minerals

Alcohol

In chemistry, an *alcohol* is any organic compound in which a hydroxyl group (-OH) is bound to a carbon atom of an alkyl or substituted alkyl group. The general formula for a simple acyclic alcohol is $C_nH_{2n+1}OH$.

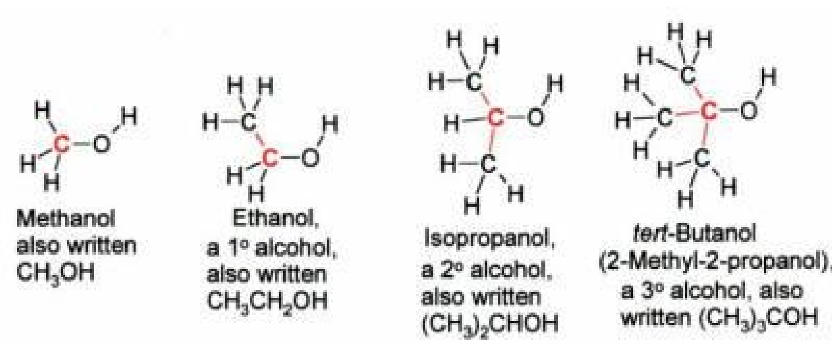
In general usage, *alcohol* refers almost always to ethanol, also known as *grain alcohol*, a strongly-smelling, colorless, volatile liquid formed by the fermentation of sugars. It also often refers to any beverage that contains ethanol (see alcoholic beverage). This sense underlies the term alcoholism (addiction to alcohol). Other forms of alcohol are usually described with a clarifying adjective, as in isopropyl alcohol or by the suffix -ol, as in isopropanol.

Structure

The functional group of an alcohol is a hydroxyl group bonded to an sp^3 hybridized carbon. It can therefore be regarded as a derivative of water, with an alkyl group replacing one of the hydrogens. If an aryl group is present rather than an alkyl, the compound is generally called a phenol rather than an alcohol. Also, if the hydroxyl group is bonded to one of the sp^2 hybridized carbons of an alkenyl group, the compound is referred to as an enol. The oxygen in an alcohol has a bond angle of around 109° (c.f. 104.5° in water), and two nonbonded electron pairs. The O-H bond in methanol (CH3OH) is around 96 picometres long.

Primary, secondary, and tertiary alcohols

There are three major subsets of alcohols- 'primary' (1°), 'secondary' (2°) and 'tertiary' (3°), based upon the number of carbons the C-OH carbon (shown in red) is bonded to. Methanol is the simplest 'primary' alcohol. The simplest secondary alcohol is isopropanol (propan-2-ol), and a simple tertiary alcohol is tert-butanol (2-methylpropan-2-ol).



The phenols with parent compound phenol have a hydroxyl group (attached to a benzene ring) just like alcohols but differ sufficiently in properties to warrant a separate treatment.

Methanol and ethanol

The simplest and most commonly used alcohols are methanol (common name methyl alcohol) and ethanol (ethyl alcohol), with the structures shown above. Methanol was formerly obtained by the distillation of wood and called "wood alcohol." It is now a cheap commodity, the chemical product of carbon monoxide reacting with hydrogen under high pressure. In common usage, "alcohol" often refers to ethanol or "grain alcohol." Methylated spirits ("Meths"), also called "surgical spirits," is a form of ethanol rendered undrinkable by

the addition of methanol. Aside from its primary use in alcoholic beverages, ethanol is also used as a highly controlled industrial solvent and raw material.

Automotive

Alcohol is often used as a automotive fuel. Ethanol and methanol can be made to burn more cleanly than gasoline or diesel. Alcohol was once commonly used as an antifreeze in automobile radiators. And to add to an internal combustion engines performance Methanol may be injected into turbocharged and supercharged engines to cool the air intake charge. Doing this provides a denser air charge.

Scientific, medical, and industrial

Alcohols are in wide use in industry and science as reagents solvents. Because of its low toxicity and ability to dissolve non-polar substances, ethanol is often used as a solvent in medical drugs, perfumes, and vegetable essences such as vanilla. In organic synthesis, alcohols frequently serve as versatile intermediates.

Ethanol is often used as an antiseptic, to disinfect the skin before injections are given, often along with iodine. Ethanol-based soaps are now becoming commonplace within restaurants and are particularly convenient as they do not require drying due to the volatility of the molecule.

Cuisine

In the kitchen, alcoholic beverages are added to dishes not only for their inherent flavors, but also because the alcohol dissolves flavor compounds that water cannot.

Ethanol is commonly used in beverages to promote flavor, reduce social inhibitions, or induce a euphoric intoxication commonly known as drunkenness.

Effects of alcohol on the body

Ethanol is a drug, with potential for overdose or toxic poisoning if taken in excessive quantities. Alcoholism, the physiological or psychological dependency on ethanol, is one of the most common drug addictions (caffeine causes chemical dependency, but not the mental longing known as addiction) in the world. Upon cessation or decrease of use, the physiological dependency can lead to physical withdrawal symptoms, such as restlessness, trouble sleeping, "the shakes," or even death. Not everyone who abuses alcohol becomes physiologically dependent upon it, but can become psychologically addicted to it, similar to marijuana. Psychological addiction produces no physical withdrawal symptoms upon cessation of drinking alcohol, but the urge, or craving, to drink again can become quite intense and irresistible.

Alcohol and politics

Ethanol for consumption has been regulated by taxation. Those who manufacture it for other purposes often avoid this expense by "denaturing" it in a manner that renders it unfit for drinking. A common way to do this is by the addition of denatonium benzoate or methanol. "SD-40" and "SD Alcohol" sometimes followed by "40-B" are designations that were established by the United States' Bureau of Alcohol, Tobacco, Firearms and Explosives for this formulation.

Sources

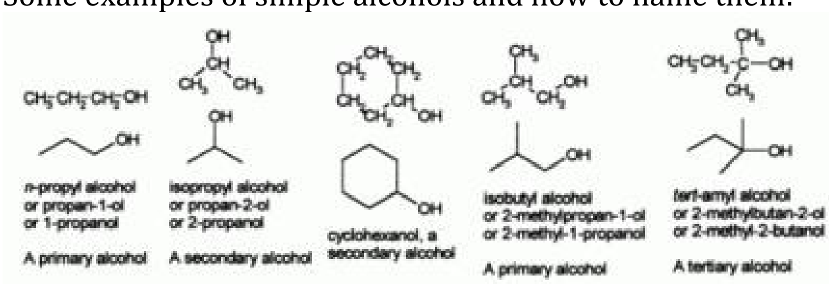
Many alcohols can be created by fermentation of fruits or grains with yeast, but only ethanol is commercially produced this way — chiefly for fuel and drink. Other alcohols are generally produced by synthetic routes from natural gas, petroleum, or coal feed stocks; for example, via acid catalyzed hydration of alkenes.

Nomenclature

Systematic names

In the IUPAC system, the name of the alkane chain loses the terminal "e" and adds "ol", e.g. "methanol" and "ethanol". When necessary, the position of the hydroxyl group is indicated by a number between the alkane name and the "ol": propan-1-ol for CH3CH2CH2OH, propan-2-ol for CH3CH(OH)CH3. Sometimes, the position number is written before the IUPAC name: 1-propanol and 2-propanol. If a higher priority group is present (such as an aldehyde, ketone or carboxylic acid), then it is necessary to use the prefix "hydroxy", for example: 1-hydroxy-2-propanone (CH_3COCH_2OH).

Some examples of simple alcohols and how to name them:



Common names for alcohols usually take the name of the corresponding alkyl group and add the word "alcohol", e.g. methyl alcohol, ethyl alcohol or tert-butyl alcohol. Propyl alcohol may be n-propyl alcohol or isopropyl alcohol depending on whether the hydroxyl group is bonded to the 1st or 2nd carbon on the propane chain. Isopropyl alcohol is also occasionally called sec-propyl alcohol.

As mentioned above alcohols are classified as primary (1°), secondary (2°) or tertiary (3°), and common names often indicate this in the alkyl group prefix. For example $(CH_3)_3COH$ is a tertiary alcohol is commonly known as tert-butyl alcohol. This would be named 2-methylpropan-2-ol under IUPAC rules, indicating a propane chain with methyl and hydroxyl groups both attached to the middle (#2) carbon.

An alcohol with two hydroxyl groups is commonly called a "glycol", e.g. HO-CH**2**-CH**2**-OH is ethylene glycol. The IUPAC name is ethane-1,2-diol, "diol" indicating two hydroxyl groups, and 1,2 indicating their bonding positions. Geminal glycols (with the two hydroxyls on the same carbon atom), such as ethane-1,1-diol, are generally unstable. For three or four groups, "triol" and "tetraol" are used.

Etymology

The word "alcohol" almost certainly comes from the Arabic language (the "al-" prefix being the Arabic definite article); however, the precise origin is unclear. It is likely that a Persian physician named Rhazes discovered this substance, but as he spoke Arabic under Arab rule, the word remains of Arabic origin. It was introduced into Europe, together with the art of distillation and the substance itself, around the 12th century by various European authors who translated and popularized the discoveries of Islamic alchemists [1].

A popular theory, found in many dictionaries, is that it comes from 'DC-D al-ku%l, originally the name of very finely powdered antimony sulfide Sb2S3 used as an antiseptic and eyeliner. The powder is prepared by sublimation of the natural mineral stibnite in a closed vessel. According to this theory, the meaning of alkuhul would have been first extended to distilled substances in general, and then narrowed to ethanol. This conjectured etymology has been circulating in England since 1672 at least (OED).

However, this derivation is suspicious since the current Arabic name for alcohol, 'DC-HD al-ku%kl, does not derive from al-ku%l. The Qur'an, in verse 37:47, uses the word 'D:HD al-ghawl — properly meaning "spirit" or "demon" — with the sense "the thing that gives the wine its headiness". The word al-ghawl is also the origin of the English word "ghoul", and the name of the star Algol. This derivation would, of course, be consistent with the use of "spirit" or "spirit of wine" as synonymous of "alcohol" in most Western languages. (Incidentally, the etymology "alcohol" = "the devil" was used in the 1930s by the U.S. Temperance movement for propaganda purposes.)

According to the second theory, the popular etymology and the spelling "alcohol" would not be due to generalization of the meaning of al-ku%l, but rather to Western alchemists and authors confusing the two words al-ku%l and al-ghawl, which have indeed been transliterated in many different and overlapping ways.

Physical and chemical properties

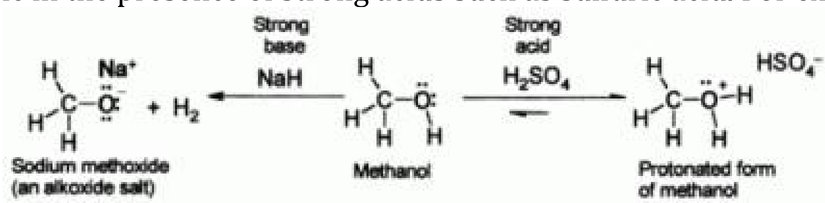
The hydroxyl group generally makes the alcohol molecule polar. Those groups can form hydrogen bonds to one another and to other compounds. Two opposing solubility trends in alcohols are: the tendency of the polar OH to promote solubility in water, and of the carbon chain to resist it. Thus, methanol, ethanol, and propanol are miscible in water because the hydroxyl group wins out over the short carbon chain. Butanol, with a four-carbon chain, is moderately soluble because of a balance between the two trends. Alcohols of five or more carbons (Pentanol and higher) are effectively insoluble because of the hydrocarbon chain's dominance.

Because of hydrogen bonding, alcohols tend to have higher boiling points than comparable hydrocarbons and ethers. The boiling point of the alcohol Ethanol is 78.29 °C, compared to 69 °C for the hydrocarbon Hexane (a common constituents of gasoline), and 34.6 °C for Diethyl ether. All simple alcohols are miscible in organic solvents. This hydrogen bonding means that alcohols can be used as protic solvents.

The lone pairs of electrons on the oxygen of the hydroxyl group also makes alcohols nucleophiles.

Alcohols, like water, can show either acidic or basic properties at the O-H group. With a pK***a*** of around 16-19 they are generally slightly weaker acids than water, but they are still able to react with strong bases such as sodium hydride or reactive metals such as sodium. The salts that result are called *alkoxides*, with the general formula RO- M+.

Meanwhile the oxygen atom has lone pairs of nonbonded electrons that render it weakly basic in the presence of strong acids such as sulfuric acid. For example, with methanol:



Alcohols can also undergo oxidation to give aldehydes, ketones or carboxylic acids, or they can be dehydrated to alkenes. They can react to form ester compounds, and they can (if activated first) undergo nucleophilic substitution reactions. For more details see the reactions of alcohols section below.

Toxicity

Alcohols often have an odor described as 'biting' that 'hangs' in the nasal passages. Ethanol in the form of alcoholic beverages has been consumed by humans since pre-historic times, for a variety of hygienic, dietary, medicinal, religious, and recreational reasons. While infrequent consumption of ethanol in small quantities may be harmless or even beneficial, larger doses result in a state known as drunkenness or intoxication (which may lead to a hangover the next day) and, depending on the dose and regularity of use, can cause acute respiratory failure or death and with chronic use has medical repercussions. Alcohol has also been known to be a catalyst for reckless behaviors that may have undesirable results, such as accidents, fighting, and unprotected sex. The LD50 of ethanol in rats 11,300 mg/kg.[2] This ratio would correspond to an 80kg (176.4lb) man drinking 65 shots of 80 proof alcohol, although the LD***50*** does not necessarily translate directly to humans.

Other alcohols are substantially more poisonous than ethanol, partly because they take much longer to be metabolized, and often their metabolism produces even more toxic substances. Methanol, or wood alcohol, for instance, is oxidized by alcohol dehydrogenase enzymes in the liver to the poisonous formaldehyde, which can cause blindness or death.

An effective treatment to prevent formaldehyde toxicity after methanol ingestion is to administer ethanol. Alcohol dehydrogenase has a higher affinity for ethanol, thus preventing methanol from binding and acting as a substrate. Any remaining methanol will then have

time to be excreted through the kidneys. Remaining formaldehyde will be converted to formic acid and excreted.

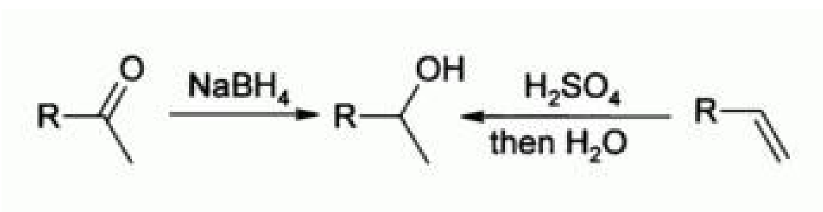
Preparation of alcohols

Laboratory

Several methods exist for the preparation of alcohols in the laboratory.

- Primary alkyl halides react with aqueous NaOH or KOH mainly to primary alcohols in nucleophilic aliphatic substitution. (Secondary and especially tertiary alkyl halides will give the elimination (alkene) product instead).
Aldehydes or ketones are reduced with sodium borohydride or lithium aluminium hydride (after an acidic workup). Another reduction by aluminumisopropylates is the Meerwein-Ponndorf-Verley reduction.
Alkenes engage in an acid catalysed hydration reaction using concentrated sulfuric acid as a catalyst which gives usually secondary or tertiary alcohols.
The hydroboration-oxidation and oxymercuration-reduction of alkenes are more reliable in organic synthesis.
Grignard reagents react with carbonyl groups to secondary and tertiary alcohols
Noyori asymmetric hydrogenation is the asymmetric reduction of ²-keto-esters

The formation of a secondary alcohol via reduction and hydration is shown:



Industrial

Industrially alcohols are produced in several ways:

- By fermentation using glucose produced from sugar from the hydrolysis of starch, in the presence of yeast and temperature of less than 37°C to produce ethanol. For instance the conversion of invertase to glucose and fructose or the conversion of glucose to zymase and ethanol.
By direct hydration using ethene or other alkenes from cracking of fractions of distilled crude oil. Uses a catalyst of phosphoric acid under high temperature and pressure.
Methanol is producted from water gas: It is manufactured from synthesis gas, where carbon monoxide and 2 equivalents of hydrogen gas are combined to produce methanol using a copper, zinc oxide and aluminium oxide catalyst at 250°C and a pressure of 50-100 atm.

Reactions of alcohols

Deprotonation

Alcohols can behave as weak acids, undergoing deprotonation. The deprotonation reaction to produce an alkoxide salt is either performed with a strong base such as sodium hydride or n-butyllithium, or with sodium or potassium metal.

2 R-OH + 2 NaH ’ 2 R-O-Na+ + H*2*‘ 2 R-OH + 2Na ’ 2R-ONa + H*2* E.g. 2 CH_3CH_2-OH + 2 Na ’ 2 CH*3*-CH*2*-ONa + H*2*

Water is similar in pK*a* to many alcohols, so with sodium hydroxide there is an equilibrium set up which usually lies to the left:

R-OH + NaOH <=> R-O-Na+ + H*2*O (equilibrium to the left)

It should be noted, though, that the bases used to deprotonate alcohols are strong themselves. The bases used and the alkoxides created are both highly moisture sensitive chemical reagents.

The acidity of alcohols is also affected by the overall stability of the alkoxide ion. Electron-withdrawing groups attached to the carbon containing the hydroxyl group will serve to stabilize the alkoxide when formed, thus resulting in greater acidity. On the other hand, the presence of electron-donating group will result in a less stable alkoxide ion formed. This will result in a scenario whereby the unstable alkoxide ion formed will tend to accept a proton to reform the original alcohol.

With alkyl halides alkoxides give rise to ethers in the Williamson ether synthesis.

Nucleophilic substitution

The OH group is not a good leaving group in nucleophilic substitution reactions, so neutral alcohols do not react in such reactions. However if the oxygen is first protonated to give ROH2+, the leaving group (water) is much more stable, and nucleophilic substitution can take place. For instance, tertiary alcohols react with hydrochloric acid to produce tertiary alkyl halides, where the hydroxyl group is replaced by a chlorine atom. If primary or secondary alcohols are to be reacted with hydrochloric acid, an activator such as zinc chloride is needed. Alternatively the conversion may be performed directly using thionyl chloride.[1]

Alcohols may likewise be converted to alkyl bromides using hydrobromic acid or phosphorus tribromide, for example:

$3\ R\text{-}OH + PBr_3$ ’ $3\ RBr + H_3PO_3$

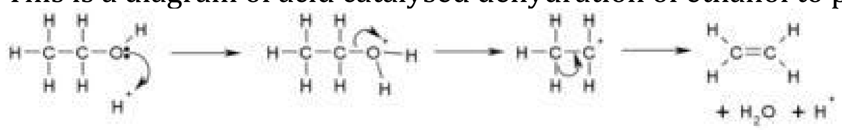
In the Barton-McCombie deoxygenation an alcohol is deoxygenated to an alkane with tributyltin hydride or a trimethylborane-water complex in a radical substitution reaction.

Dehydration

Alcohols are themselves nucleophilic, so ROH_2^+ can react with ROH to produce ethers and water in a dehydration reaction, although this reaction is rarely used except in the manufacture of diethyl ether.

More useful is the E1 elimination reaction of alcohols to produce alkenes. The reaction generally obeys Zaitsev's Rule, which states that the most stable (usually the most substituted) alkene is formed. Tertiary alcohols eliminate easily at just above room temperature, but primary alcohols require a higher temperature.

This is a diagram of acid catalysed dehydration of ethanol to produce ethene:



A more controlled elimination reaction is the Chugaev elimination with carbon disulfide and iodomethane.

Esterification

To form an ester from an alcohol and a carboxylic acid the reaction, known as Fischer esterification, is usually performed at reflux with a catalyst of concentrated sulfuric acid:

$R\text{-}OH + R'\text{-}COOH$ ’ $R'\text{-}COOR + H_2O$

In order to drive the equilibrium to the right and produce a good yield of ester, water is usually removed, either by an excess of H_2SO_4 or by using a Dean-Stark apparatus. Esters may also be prepared by reaction of the alcohol with an acid chloride in the presence of a base such as pyridine.

Other types of ester are prepared similarly- for example tosyl (tosylate) esters are made by reaction of the alcohol with p-toluenesulfonyl chloride in pyridine.

Oxidation

Primary alcohols generally give aldehydes or carboxylic acids upon oxidation, while secondary alcohols give ketones. Traditionally strong oxidants such as the dichromate ion or potassium permanganate are used, under acidic conditions, for example:

$3\ CH_3\text{-}CH(\text{-}OH)\text{-}CH_3 + K_2Cr_2O_7 + 4\ H_2SO_4$ ’ $3\ CH_3\text{-}C(=O)\text{-}CH_3 + Cr_2(SO_4)_3 + K_2SO_4 + 7\ H_2O$

Frequently in aldehyde preparations these reagents cause a problem of over-oxidation to the carboxylic acid. To avoid this, other reagents such as PCC, Dess-Martin periodinane, 2-Iodoxybenzoic acid, TPAP or methods such as Swern oxidation and Corey-Kim oxidation are now preferred. In the Guerbet reaction aliphatic alcohols dimerize with an initial oxidation step.

Alcohols with a methyl group attached to the alcohol carbon can also undergo a haloform reaction (such as the iodoform reaction) in the presence of the halogen and a base such as sodium hydroxide.

Tertiary alcohols resist oxidation, but can be oxidised by reagents such as 2,3-dichloro-5,6-dicyano-1,4-benzoquinone.

Boric acid

Boric acid

General

Other names Orthoboric acid, Boracic acid, Sassolite, Optibor®, Borofax®

Molecular formula H_3BO_3

Molar mass 61.832 g/mol

Appearance White crystalline liquid

CAS number [10043-35-3]

Properties

Density and phase 1.435 g/cm^3, solid.

Solubility in water 5.7 g/100 ml (25°C)

Melting point 169°C decomp.

Acidity (p*Ka*) 9.24 (see text)

Structure

Molecular shape Planar

Dipole moment Zero

Thermodynamic data

Standard enthalpy of formation ”*f*Ho*solid* 1093.99 kJ/mol

Standard molar entropy So*solid*

88.7 J.K1.mol1

Hazards

MSDS External MSDS

EU classification N/A

Non-flammable.

Related compounds

Related compounds Boron trioxide, Borax

Except where noted otherwise, data are given for materials in their standard state (at 25°C, 100 kPa)

Boric acid, also called *boracic acid* or *orthoboric acid*, is a mild acid often used as an antiseptic, insecticide, flame retardant, in nuclear power plants to control the fission rate of uranium, and as a precursor of other chemical compounds. It exists in the form of colorless crystals or a white powder and dissolves in water. It has the chemical formula H_3BO_3, sometimes written $B(OH)_3$. When occurring as a mineral, it is called sassolite.

Preparation

Boric acid is produced mainly from borate minerals by the reaction with sulfuric acid. The largest source of borates in the world is an open-pit mine in Death Valley, California, USA.

Properties

Boric acid was first prepared by Wilhelm Homberg (1652-1715) from borax, by the action of mineral acids, and was given the name sal sedativum Hombergi. The presence of boric acid or its salts has been noted in sea-water, whilst it is also said to exist in plants and especially in almost all fruits (A. H. Allen, Analyst, 1904, 301). The free acid is found native in certain volcanic districts such as Tuscany, the Lipari Islands and Nevada, issuing mixed with steam from fissures in the ground; it is also found as a constituent of many minerals (borax, boracite, boronatrocaicite and colemanite).Boric acid is soluble in boiling water. When heated above 170°C it dehydrates, forming *metaboric acid* HBO_2. Metaboric acid is a white, cubic crystalline solid and is only slightly soluble in water. It melts at about 236°C, and when heated above about 300°C further dehydrates, forming *tetraboric acid* or *pyroboric acid*, $H_2B_4O_7$. Boric acid can refer to any of these compounds. Further heating leads to boron trioxide.

Boric acid does not dissociate in aqueous solution, but is acidic due to its interaction with water molecules:

$B(OH)_3 + H_2O$ Ì $B(OH)_4 + H^+$ $K_a = 5.8x10^{10}$ L/mol; $pK_a = 9.24$.

Polyborate anions are formed at pH 7–10 if the boron concentration is higher than about 0.025 mol/L. The best known of these is the *tetraborate* ion, found in the mineral borax:

$4B(OH)_4 + 2H^+$ Ì $B_4O_7^2 + 9H_2O$

Uses

It can be used as an antiseptic for minor burns or cuts and is sometimes used in dressings or salves or is applied in a very dilute solution as an eye wash. It is poisonous if taken internally or inhaled, although it is generally not considered to be much more toxic than table salt (based on its mammal LD50 rating of 2660mg/kg body mass).

Boric acid can be used to treat yeast and fungal infections such as candidiasis (vaginal yeast infections) by filling gelcaps with boric acid powder and inserting two into the vaginal canal at bedtime for three to four nights in a row. It is also used as prevention of athlete's foot, by inserting powder in the socks or stockings, and in solution can be used to treat some kinds of otitis externa (ear infection) in both humans and animals. The preservative in urine sample bottles (red cap) in the UK is Boric acid.

It is often used as a relatively nontoxic insecticide, for killing cockroaches, termites, fire ants, fleas, and many other insects. It can be used directly in powdered form for fleas and cockroaches, or mixed with sugar or grape jelly for ants. It is also a component of many commercial insecticides. In this use, especially in the case of cockroaches, the boric acid in the form of a powder is applied to areas frequented by the insects. The lightweight particles cling to the legs of the insects and eventually cause fatal chemical burns. Boric acid for this use in residential apartments is sold commercially in urban areas afflicted with cockroaches.

Boric acid is used in nuclear power plants to slow down the rate at which fission is occurring. Fission chain reactions are generally driven by the amount of neutrons present (as products from previous fissions). Boron has a high cross-section for absorption of neutrons and is therefore dissolved into the primary coolant which circulates through the reactor. By changing the concentration of boric acid in the water, fission can be regulated. Boron is also dissolved into the spent fuel pools containing used uranium rods. The concentration is high enough to keep fissions at a minimum.

In the jewelry industry, boric acid is often used in combination with denatured alcohol to reduce surface oxidation and firescale from forming on metals during annealing and soldering operations.

Borates including boric acid have been used since the time of the Greeks for cleaning, preserving food, and other activities.

Lithium boric acid is the lithium salt of boric acid and is used in the laboratory as buffer for gel. TBE buffer is widely used for the electrophoresis of nucleic acids and has a higher buffer capacity than a TAE Buffer. It can be used for DNA and RNA polyacrylamide and agarose gel electrophoresis.

It is used in pyrotechnics to prevent the amide-forming reaction between aluminum and nitrates. A small amount of boric acid is added to the composition to neutralize alkaline amides that can react with the aluminum.

It is also used in India and across the world to dust down Carrom Boards to decrease friction and increase speed of play.

References

- Jolly, W. L. (1991). Modern Inorganic Chemistry (2nd Edn.). New York: McGraw-Hill. ISBN 0-07-112651-1.

Calcium hypochlorite

Systematic name Calcium hypochlorite

Other names HTH

Molecular formula $Ca(ClO)_2$

Molar mass 143.1 g/mol

Calcium hypochlorite is a chemical compound with formula $Ca(ClO)_2$. It is widely used for water treatment and as a bleaching agent (bleaching powder). This chemical is considered to be relatively stable and has greater available chlorine than sodium hypochlorite (liquid bleach).

Preparation

It is manufactured using the calcium process and sodium process. Or it can be prepared by the action of slaked lime on chlorine:

$Ca(OH)_2 + Cl_2$ ’ $Ca(OCl)_2 + H_2$

Bleaching powder is actually a mixture of calcium hypochlorite $Ca(OCl)_2$ and the basic chloride $CaCl_2$, $Ca(OH)_2$, H_2O with some slaked lime, $Ca(OH)_2$.

Properties

It is a yellow white solid which has a strong smell of chlorine. Calcium hypochlorite is not highly soluble in water. For that reason it should preferably be used in soft to middle hard water. There are two types of calcium hypochlorite - a dry form and a hydrated form. The hydrated form is safer to handle.

Calcium hypochlorite reacts with carbon dioxide to form calcium carbonate and release chlorine:

$Ca(OCl)_2 + CO_2$ ’ $CaCO_3 + Cl_2$

Calcium hypochlorite reacts with hydrochloric acid to form calcium chloride:

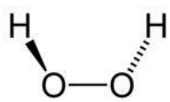
$Ca(OCl)_2 + 2\ HCl$ ’ $CaCl_2 + H_2O + Cl_2$

Uses

Calcium hypochlorite is used for the disinfection of drinking water or swimming pool water. For use in outdoor swimming pools, calcium hypochlorite can be used as a sanitiser in combination with a cyanuric acid stabiliser. The stabiliser will reduce the loss of chlorine because of UV radiation.

Calcium hypochlorite (known as 'bleaching powder') is also used for bleaching cotton and linen and used in the manufacture of chloroform.

Hydrogen peroxide



Systematic name Dihydrogen dioxide

Other names Hydrogen peroxide, hydrogen dioxide

Molecular formula H_2O_2

Molar mass 34.0147 g/mol.

Appearance Very pale blue color; colorless in solution.

CAS number [7722-84-1] [1]

Properties

Density and phase 1.4 g/cm^3, liquid

Solubility in water Miscible.

Melting point -11 °C (262.15 K)

Boiling point 150.2 °C (423.35 K)

Acidity (pK_a) 11.65

Viscosity 1.245 cP at 20 °C

Structure

Dipole moment 2.26 D

Hazards

MSDS

30% hydrogen peroxide msds
60% hydrogen peroxide msds

Main hazards Oxidant, corrosive.

Flash point Non-flammable.

R/S statement R: **R5**, **R8**, **R20**, **R22**,**R35** S: **S1**, **S2**, **S17**, **S26**,**S28**, **S36**, **S37**, **S39**, **S45**

RTECS number MX0900000

Related compounds

Other cations Sodium peroxide

Related compounds water, ozone, hydrazine

Except where noted otherwise, data are given for materials in their standard state (at 25°C, 100 kPa)

Hydrogen peroxide (H_2O_2) is a very pale blue liquid which appears colourless in a dilute solution, slightly more viscous than water. It has strong oxidizing properties and is therefore a powerful bleaching agent that has found use as a disinfectant, as an oxidizer, and in rocketry (particularly in high concentrations as high-test peroxide (HTP) as a monopropellant), and in bipropellant systems.

History

Hydrogen peroxide was first isolated in 1818 by Louis Jacques Thénard by reacting barium peroxide with nitric acid. An improved version of this process used hydrochloric acid, followed by sulfuric acid to precipitate the barium chloride byproduct. Thenard's process was used from the end of the 19th century until the middle of the 20th century. [1] Modern manufacture methods are discussed below.

Uses

Industrial applications

About 50% of the world's production of hydrogen peroxide in 1994 was used for pulp- and paper-bleaching. Other bleaching applications are becoming more important as

hydrogen peroxide is seen as an environmentally-benign alternative to chlorine-based bleaches.

Other major industrial applications for hydrogen peroxide include the manufacture of sodium percarbonate and sodium perborate, used as mild bleaches in laundry detergents. It is used in the production of certain organic peroxides such as dibenzoyl peroxide, used in polymerisations and other chemical processes. Hydrogen peroxide is also used in the production of epoxides such as propylene oxide. Reaction with carboxylic acids produces a corresponding "per-acid". Peracetic acid and meta-chloroperoxybenzoic acid (commonly abbreviated mCPBA) are prepared from acetic acid and meta-chlorobenzoic acid, respectively. The latter is commonly reacted with alkenes to give the corresponding epoxide.

Domestic uses

Diluted H_2O_2 (around 5%) is used to bleach human hair, hence the phrases *peroxide blonde* and *bottle blonde*. It can absorb into skin upon contact and create a local skin capillary embolism which appears as a temporary whitening of the skin. It whitens skeletons that are to be put on display. 3% H2O2 is used medically for cleaning wounds, removing dead tissue, or as an oral debriding agent. Most over-the-counter peroxide solutions are not, however, suitable for ingestion.

The Food and Drug Administration (FDA) has classified hydrogen peroxide as a Low Regulatory Priority (LRP) drug for use in controlling fungus on fish and fish eggs.

Some gardeners and hydroponics implementers have professed the value of hydrogen peroxide in their watering solutions. They claim its spontaneous decomposition releases oxygen to the plant that can enhance root development and also help treat root rot, which is cellular root death due to lack of oxygen. Laboratory tests conducted by fish culturists in recent years have demonstrated that common household hydrogen-peroxide can be used safely to provide oxygen for small fish. Citation Reference Hydrogen-peroxide releases oxygen by decomposition when it is exposed to catalysts.

Hydrogen peroxide is increasingly popular for the treatment of hydrogen sulfide and iron. Catalytic carbon and redox media perform well with hydrogen peroxide pretreatment. Generally 90% of the reaction between hydrogen peroxide and hydrogen sulfide takes place within 10 to 15 minutes, with the balance reacting in an additional 20 to 30 minutes. The sulfur in hydrogen sulfide H_2S) is in the -2 state. In a neutral solution, hydrogen peroxide will oxidize hydrogen sulfide to elemental sulfur via the following reaction: 8 H_2S(g) + 8 H_2O_2(aq) ’ S_8(s) + 16 H_2O(l)

The reaction is slow but may be catalyzed by metal ions. To be more specific for doses of chemical feed levels for oxidation of iron, manganese and hydrogen sulfide in domestic water supplies, here are some figures: Iron: For each ppm Fe feed = 0.3 - 0.5 ppm, 20 minutes Manganese: For each ppm Mn feed = 0.8 - 1.0 ppm, 20 minutes Hydrogen Sulfide: For each ppm H2S feed = 1.0 - 1.5 ppm, 30 minutes (all above figures are for minimum retention time). When more than one constituent is to be oxidized (i.e. iron & H_2S) add the above values to determine the total ppm feed needed to oxidize two or more.

Hydrogen peroxide is a strong oxidizer effective in controlling sulfide and organic related odors in wastewater collection and treatment systems. It is typically applied to a wastewater

system most frequently where there is a retention time of less than five hours and at least 30 minutes prior to the point where the hydrogen sulfide is released. Hydrogen peroxide will oxidize the hydrogen sulfide present and in addition promote bio-oxidation of organic odors. Hydrogen peroxide decomposes to oxygen and water adding dissolved oxygen to the system thereby reducing Biological Oxygen Demand (BOD).

Commercial peroxide, as bought at the drugstore in a 2.5%-3% solution, can be used to remove bloodstains from carpets and clothing. If a few tablespoons of peroxide are poured onto the stain, they will bubble up in the area of the blood. After a few minutes the excess liquid can be wiped up with a cloth or paper towel and the stain will be gone. Care should be taken, however, as hydrogen peroxide will bleach or discolor many fabrics.

Hydrogen peroxide is used in glow sticks as an oxidising agent. It reacts with phenyl oxalate ester to form an unstable CO_2 dimer which in turn causes an added dye to reach an excited state, the latter relaxing to release photons of light.

Storage

Small quantities of many different concentrations and grades can be legally stored and used with few regulations.

Hydrogen peroxide should be stored in a container made from a material that doesn't react with the chemical. Numerous materials and processes are available, and these vary based on the concentration and grade (purity) of the hydrogen peroxide. In general, it is an oxidizer and should be stored away from fuel sources and sources of catalytic contamination. Because oxygen is formed during the natural decomposition of the peroxide, the resulting increase in pressure can cause a glass container to break. Therfore, H_2O_2 should be stored in vented plastic containers.

Use as propellant

H_2O_2 can be used either as a monopropellant (not mixed with fuel) or as the oxidizer component of a bipropellant rocket. Use as a monopropellant takes advantage of the decomposition of 70–98+% concentration hydrogen peroxide into steam and oxygen. The propellant is pumped into a reaction chamber where a catalyst (usually a silver or platinum screen) triggers decomposition, and the hot (>600 °C) oxygen/steam produced is used directly for thrust. H2O2 monopropellant produces a maximum specific impulse (Isp) of 161 s (1.6 kN·s/kg), which makes it a low-performance monopropellant. Compared to hydrazine, peroxide is less toxic, but it is also much less powerful. The famous Bell Rocket Belt used hydrogen peroxide monopropellant.

As a bipropellant, H_2O_2 is decomposed to burn a fuel as an oxidizer. Specific impulses as high as 350 s (3.5 kN·s/kg) can be achieved, depending on the fuel. Peroxide used as an oxidizer gives a somewhat lower I_{sp} than liquid oxygen, but is dense, storable, noncryogenic and can be more easily used to drive gas turbines to give high pressures. It also can be used for regenerative cooling of rocket engines. Peroxide was used very successfully as an oxidizer for early World-War-II era German rockets, and for the low-cost British launchers, Black Knight and Black Arrow.

In the 1940s and 1950s, the Walter turbine used hydrogen peroxide for use in submarines while submerged; it was found to be too noisy and maintenance-demanding compared to the conventional diesel-electric power system. Some torpedoes used hydrogen peroxide as oxidizer or propellant, but this use has been discontinued by most navies for safety reasons. Hydrogen peroxide leaks were blamed for the sinkings of HMS Sidon and the Russian submarine Kursk. It was discovered, for example, by the Japanese Navy in torpedo trials, that the concentration of H_2O_2 in right-angle bends in HTP pipework can often lead to explosions in submarines and torpedoes.

While its application as a monopropellant for large engines has waned, small thrusters for attitude control that run on hydrogen peroxide are still in use on some satellites, and provide benefits on the spacecraft, making it easier to throttle and safer loading and handling of fuel before launch (as compared to hydrazine monopropellant). However, hydrazine is a more popular monopropellent in spacecraft because of its higher specific impulse and lower rate of decomposition.

Recently, H2O2/propylene as an approach to inexpensive Single Stage To Orbit has been proposed; this involves a main fuel tank containing propylene, with a bladder floating in it containing the H2O2. This combination offers 15% superior ISP to O2/RP4 (a kerosene used as rocket propellant), avoiding the need for turbines, cryogenic storage or hardware, and greatly reduced cost for the construction of the booster; the potential of this and other alternate systems is discussed in some detail at Dunn Engineering which is offered as a citation.

Therapeutic use

Hydrogen peroxide has been used as an antiseptic and anti-bacterial agent for many years. While its use has decreased in recent years due to the popularity of better-smelling and more readily-available over the counter products, it is still used by many hospitals, doctors and dentists in sterilising, cleaning and treating everything from floors to Root canal procedures.

Recently, alternative medical practitioners have advocated administering doses of hydrogen peroxide intravenously in extremely low (less than one percent) concentrations for hydrogen peroxide therapy — a controversial alternative medical treatment for cancer. However, according to the American Cancer Society, "there is no scientific evidence that hydrogen peroxide is a safe, effective or useful cancer treatment." They advise cancer patients to "remain in the care of qualified doctors who use proven methods of treatment and approved clinical trials of promising new treatments." [2] Internal use of hydrogen peroxide has a history of causing fatal blood disorders, and its recent use as a therapeutic treatment has been linked to several deaths.[3],[4]

Hydrogen peroxide is GRAS (Generally Recognised As Safe) as an antimicrobial agent, an oxidizing agent and more by the US Food and Drug Administration.[5] Hydrogen peroxide can also be used as a toothpaste when mixed with correct quantities of baking soda and salt.[6] Like benzoyl peroxide, hydrogen peroxide is also sometimes used in the treatment of acne.

Hydrogen peroxide is also used as an emetic in veterinary practice.[7]

Physical properties

Hydrogen peroxide adopts a "skewed" shape, due to repulsion between the lone pairs on the oxygen atoms. Despite the fact that the O-O bond is a single bond, the molecule has a remarkably high barrier to complete rotation of 29.45 kJ/mol (compared with 12.5 kJ/mol for the rotational barrier of ethane). The increased barrier is also attributed to lone-pair lone-pair repulsion. The bond angles are affected by hydrogen bonding, which is relevant to the structural difference between gaseous and crystalline forms; indeed a wide range of values is seen in crystals containing molecular H_2O_2.

Chemical properties

H_2O_2 is one of the most powerful oxidizers known -- stronger than chlorine, chlorine dioxide, and potassium permanganate. And through catalysis, H_2O_2 can be converted into hydroxyl radicals (.OH) with reactivity second only to fluorine.

Oxidant - Oxidation potential, V

Fluorine 3.0

Hydroxyl radical 2.8

Ozone **2.1**

Hydrogen peroxide 1.8

Potassium permanganate **1.7**

Chlorine dioxide 1.5

Chlorine 1.4

Hydrogen peroxide can decompose spontaneously into water and oxygen. It usually acts as an oxidizing agent, but there are many reactions where it acts as a reducing agent, releasing oxygen as a by-product. It also readily forms both inorganic and organic peroxides.

Decomposition

Hydrogen peroxide often decomposes (disproportionates) exothermically into water and oxygen gas spontaneously:

2 H_2O_2 ’ 2 H_2O + O_2 + Energy

This process is very favorable; it has a ”Ho of 98.2 kJ/mol and a ”Go of 119.2 kJ/mol and a ”S of 70.5 J/mol K. The rate of decomposition is dependent on the temperature and

concentration of the peroxide, as well as the pH and the presence of impurities and stabilizers. Hydrogen peroxide is incompatible with many substances that catalyse its decomposition, including most of the transition metals and their compounds. Common catalysts include manganese dioxide, potassium permanganate, and silver. The same reaction is catalysed by the enzyme catalase, found in the liver, whose main function in the body is the removal of toxic byproducts of metabolism and the reduction of oxidative stress. The decomposition occurs more rapidly in alkali, so acid is often added as a stabilizer.

Spilling high concentration peroxide on a flammable substance can cause an immediate fire fueled by the oxygen released by the decomposing hydrogen peroxide. High-strength peroxide (also called high-test peroxide, or HTP) must be stored in a vented container to prevent the buildup of oxygen gas, which would otherwise lead to the eventual rupture of the container. Any container must be made of a compatible material such as PTFE, polyethylene, stainless steel, or aluminium and undergo a cleaning process (passivation) to remove all contamination prior to the introduction of peroxide. (Note that while compatible at room temperature, polyethylene can explode with peroxide in a fire.)

In the presence of certain catalysts, such as Fe^{2+} or Ti^{3+}, the decomposition may take a different path, with free radicals such as HO· (hydroxyl) and HOO· being formed. A combination of H_2O_2 and Fe^{2+} is known as Fenton's reagent.

Redox reactions

In aqueous solution, hydrogen peroxide can oxidize or reduce a variety of inorganic ions. When it acts as a reducing agent, oxygen gas is also produced. In acid solution Fe^{2+} is oxidized to Fe^{3+},

$2\,Fe^{2+}(aq) + H_2O_2 + 2\,H^{+}(aq)$ ’ $2\,Fe^{3+}(aq) + 2H_2O(l)$

and sulfite (SO_3^2) is oxidized to sulfate (SO_4^2). However, potassium permanganate is reduced to Mn^{2+} by acidic H_2O_2. Under alkaline conditions, however, some of these reactions reverse; Mn^{2+} is oxidized to Mn^{4+} (as MnO_2), yet Fe^{3+} is reduced to Fe^{2+}.

$2\,Fe^{3+} + H_2O_2 + 2\,OH$ ’ $2\,Fe^{2+} + 2\,H_2O + O_2$

Hydrogen peroxide is frequently used as an oxidising agent in organic chemistry. One application is for the oxidation of thioethers to sulfoxides. For example, methyl phenyl sulfide was oxidised to methyl phenyl sulfoxide in 99% yield in methanol in 18 hours (or 20 minutes using a $TiCl_3$ catalyst):

$Ph\text{-}S\text{-}CH_3 + H_2O_2$ ’ $Ph\text{-}S(O)\text{-}CH_3 + H_2O$

Alkaline hydrogen peroxide is used for epoxidation of electron-deficient alkenes such as acrylic acids, and also for oxidation of alkylboranes to alcohols, the second step of hydroboration-oxidation.

Formation of peroxide compounds

Hydrogen peroxide is a weak acid, and it can form hydroperoxide or peroxide salts or derivatives of many metals. For example, with aqueous solutions of chromic acid (CrO_3), it can form an unstable blue peroxide $CrO(O_2)_2$. It can also produce peroxoanions by reaction with anions; for example, reaction with borax leads to sodium perborate, a bleach used in laundry detergents:

$Na_2B_4O_7 + 4\ H_2O_2 + 2\ NaOH \rightarrow 2\ Na_2B_2O_4(OH)_4 + H_2O$

H_2O_2 converts carboxylic acids (RCOOH) into peroxy acids (RCOOOH), which are themselves used as oxidizing agents. Hydrogen peroxide reacts with acetone to form acetone peroxide, and it interacts with ozone to form hydrogen trioxide. Reaction with urea produces carbamide peroxide, used for whitening teeth. An acid-base adduct with triphenylphosphine oxide is a useful "carrier" for H_2O_2 in some reactions.

Hydrogen peroxide reacts with ozone to form trioxidane.

Alkalinity

Hydrogen peroxide is a much weaker base than water, but it can still form adducts with very strong acids. The superacid HF/SbF_5 forms unstable compounds containing the $[H_3O_2]^+$ ion.

Manufacture

Hydrogen peroxide is manufactured today almost exclusively by the autoxidation of 2-ethyl-9,10-dihydroxyanthracene to 2-ethylanthraquinone and hydrogen peroxide using oxygen from the air. The anthraquinone derivative is then extracted out and reduced back to the dihydroxy compound using hydrogen gas in the presence of a metal catalyst. The overall equation for the process is deceptively simple:

$H_2 + O_2 \rightarrow H_2O_2$

However the economics of the process depend on effective recycling of the quinone and extraction solvents, and of the hydrogenation catalyst.

Formerly inorganic processes were used, employing the electrolysis of an aqueous solution of sulfuric acid or acidic ammonium bisulfate (NH_4HSO_4), followed by hydrolysis of the peroxydisulfate $((SO_4)_2)^{2}$ which is formed.

In 1994, world production of H_2O_2 was around 1.9 million tonnes, most of which was at a concentration of 70% or less. In that year bulk 30% H_2O_2 sold for around US \$0.54 per kg, equivalent to US \$1.50 per kg (US \$0.68 per lb) on a "100% basis".

Concentration

Hydrogen peroxide works best as a propellant in extremely high concentrations. At concentrations above approximately 67%, decomposed hydrogen peroxide will produce superheated vapors which can then be used to generate thrust, power, or work. Normal

propellant grade concentrations vary from 70 to 98% with common grades of 70, 85, 90, and 98%. Many of these grades and variations are described in detail in the United States propellant specification number MIL-P-16005 Revision F, which is currently available. The available suppliers of high concentration propellant grade hydrogen peroxide are generally one of the large commercial companies which make other grades of hydrogen peroxide; including Solvay Interox, FMC, and Degussa. Other companies which have made propellant grade hydrogen peroxide in the recent past include Air Liquide and DuPont. Note that DuPont recently sold its hydrogen peroxide manufacturing business to Degussa.

Propellant grade hydrogen peroxide is available to qualified buyers. Typically this chemical is only sold to commercial companies or government institutions which have the ability to properly handle and utilize the material.

Non-professionals have purchased 70% or lower concentration hydrogen peroxide (the remaining 30% is water with traces of impurities and stabilizing materials, such as tin salts, phosphates, nitrates, and other chemical additives), and increased its concentration themselves - a potentially extremely dangerous practice that should not be encouraged. Many amateurs try distillation, but this is extremely dangerous with hydrogen peroxide; peroxide vapor can ignite or detonate depending on specific combinations of temperature and pressure. In general any boiling mass of high concentration hydrogen peroxide at ambient pressure will produce vapor phase hydrogen peroxide which can detonate. This hazard is mitigated, but not entirely eliminated with vacuum distillation. Vacuum distillation of propellant grade hydrogen peroxide is still hazardous and is best done by qualified laboratories or companies. Other approaches for concentrating hydrogen peroxide are sparging and fractional crystallization.

High concentration hydrogen peroxide is readily available in 70, 90, and 98% concentrations in sizes of 1 gallon, 30 gallon, and bulk tanker truck volumes. Propellant grade hydrogen peroxide is being used on current military systems and is in numerous defense and aerospace research and development programs. Many privately funded rocket companies are using hydrogen peroxide, notably Blue Origin. Some amateur groups have expressed interest in manufacturing their own peroxide, for their use and for sale in small quantities to others. The production of hydrogen peroxide by amateurs is potentially dangerous to both the producers of the chemical, persons in the vicinity of the chemical, and users of the chemical.

Hazards

Hydrogen peroxide, either in pure or diluted form, can pose several risks:

- Above roughly 70% concentrations, hydrogen peroxide can give off vapor that can detonate above 70 °C (158 °F) at normal atmospheric pressure. This can then BLEVE the remaining liquid. Distillation of hydrogen peroxide at normal pressures is thus highly dangerous, and must be avoided.
- Hydrogen peroxide vapors can form sensitive contact explosives with hydrocarbons such as greases. Hazardous reactions ranging from ignition to explosion have been reported with alcohols, ketones, carboxylic acids

(particularly acetic acid), amines and phosphorus. The saying is 'peroxides kill chemists'.

- Hydrogen peroxide, if spilled on clothing (or other flammable materials), will preferentially evaporate water until the concentration reaches sufficient strength, then clothing will spontaneously ignite. Leather generally contains metal ions from the tanning process and will often catch fire almost immediately.[8]
- Concentrated hydrogen peroxide (>50%) is corrosive, and even domestic-strength solutions can cause irritation to the eyes, mucous membranes and skin. Swallowing hydrogen peroxide solutions is particularly dangerous, as decomposition in the stomach releases large quantities of gas (10 times the volume of a 3% solution) leading to internal bleeding. Severe pulmonary irritation by inhalation over 10%.

Hydrogen peroxide is naturally produced as a byproduct of oxygen metabolism, and virtually all organisms possess enzymes known as peroxidases, which apparently harmlessly catalytically decomposes low concentrations of hydrogen peroxide to water and oxygen (see Decomposition above).

In one incident, several people were injured after a hydrogen peroxide spill on board Northwest Airlines Flight 957 because they mistook it for water.

For more information on the risks of working with this chemical, consult an MSDS. It reacts to make water and oxygen gas.

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Listerine

Listerine is a brand name for antiseptic mouthwash, named after the English physician Joseph Lister (father of modern antiseptics) who had performed the first antiseptic surgery ever in 1865. Its medicinal taste is palliated slightly by a sweet flavor. Its slogan is "Kills germs that cause bad breath", though halitosis can return after use, even if nothing "extra" is placed in the mouth. This happens because saliva washes away the product, allowing the body's natural bacteria to repopulate the area.

Listerine is one of the most popular mouthwashes sold in the U.S. It is currently manufactured and distributed by Pfizer Inc, however, subject to regulatory approvals by the end of 2006, Johnson & Johnson will acquire the Listerine brand. Procter & Gamble's Scope is its main competitor.

The active ingredients are menthol, thymol, methyl salicylate, and eucalyptol, all of which are structural isomers. Ethanol or grain alcohol is present in concentrations between 21 and 26% w/v. At the concentrations in Listerine, ethanol per se does not have antimicrobial activity but rather serves to dissolve the active ingredients and to facilitate the penetration of the active ingredients into dental plaque.

Listerine has therapeutic uses that contribute to oral health when used regularly as an adjunct to mechanical oral hygiene procedures (toothbrushing and flossing). In clinical studies it has been shown that using Listerine regularly can reduce an additional 52% more plaque than merely brushing and flossing. Listerine was the first over-the-counter mouthwash to receive the American Dental Association's Seal of Acceptance for helping to control dental plaque and gingivitis. In addition, an FDA Advisory Panel has recommended that the active ingredients in Listerine be classified as Category I (safe and effective) for antiplaque and antigingivitis activity.

The Listerine brand name is also used on brands of toothpaste and on PocketPaks, a minty, dissolvable strip intended to instantly wash and refresh the mouth. In the late summer of 2005, Listerine began selling PocketMist, which is a breath-freshener in spray form.

History

First formulated by Dr Joseph Lawrence and Jordan Wheat Lambert in 1879 as a surgical antiseptic, it was given to dentists for oral care in 1895 and became the first over-the-counter mouthwash sold in the United States in 1914.

According to Freakonomics (p. 91),

Listerine was invented in the 19th century as a powerful surgical antiseptic. It was later sold, in a distilled form, as a floor cleaner and a cure for gonorrhea. But it wasn't a runaway success until the 1920s, when it was pitched as a solution for "chronic halitosis", the faux medical term that the Listerine advertising group created in 1921 to describe bad breath. By naming and thus creating a medical condition for which consumers now felt they needed a cure, Listerine created a market for their mouthwash. Until that time, bad breath was not conventionally considered a catastrophe, but Listerine's ad campaign changed that. As the advertising scholar James B. Twitchell writes, "Listerine did not make mouthwash as much as it made halitosis." Listerine's new ads featured forlorn young women and men, eager for marriage but turned off by their mate's rotten breath. "Can I be happy with him in spite of that?" one maiden asked herself. In just seven years, the company's revenues rose from $115,000 to more than $8 million.

From 1921 until the mid-1970s Listerine was also marketed as a preventive and remedy for colds and sore throats. In 1976, the Federal Trade Commission ruled that these claims were misleading, and that Listerine had "no efficacy" at either preventing or alleviating the symptoms of sore throats and colds. Warner-Lambert was ordered to stop making the claims, and to include in the next $10.2 million dollars' of Listerine ads a specific mention that "contrary to prior advertising, Listerine will not help prevent colds or sore throats or lessen their severity."

Listerine was packaged in a glass bottle inside a cardboard tube for nearly 80 years before the first revamps were made to the brand; in 1992, Cool Mint Listerine was introduced in addition to the regular Antiseptic formula, and in 1994, both brands were introduced in plastic bottles for the first time. In 2002, FreshBurst was added, then in 2003 Natural Citrus and in 2004, the ill-fated Cinnamon was released. In 2006 a new addition to the "less intense" variety, Vanilla Mint, was released. Currently, seven different kinds of Listerine are on the market in the U.S. and abroad: Original, Cool Mint, FreshBurst, Natural Citrus, Vanilla Mint, Advanced with Tartar Control, and Whitening. The most recent addition is the whitening formula.

Safety

There is no evidence that its properties as a solvent, mainly from the 26.9% (in regular Listerine) alcohol, cause an easier reception of carcinogens. In other words, repeated use of Listerine does not increase the risk of oral cancer. Both the American Dental Association (ADA) and the United States National Cancer Institute (NCI) agree that the alcohol contained in antiseptic mouthrinse is safe and not a factor in oral cancers. Specific study reviews and results can be found in clinical reports by J.G. Elmore and R.I. Horowitz ["Oral cancer and mouthwash use: Evaluation of the epidemiologic evidence." Otolaryngol Head Neck Surg. 1995;1(113):253–261] and Mashburg et al. ["A Study of the relationship between mouthwash use and oral and pharyngeal cancer." JADA, 1985.] which summarize that alcohol-containing mouth rinses are not associated with oral cancer.

Trivia

In the mid-1990s, Scope listed Rosie O'Donnell as the least-kissable celebrity in the U.S. She teamed up with Listerine to give money to charity every time she kissed someone on her talk show; this provided positive publicity for Listerine and harsh publicity for Scope, which O'Donnell disparaged on her show.

The song "Germfree Adolecents" by the 1970's punk rock group X-Ray Spex has a lyric that has often been misheard. Some will hear "Rinse your mouth with Listerine" when the lyric is actually "Rinse your mouth with glycerine".

Naphthalene

Naphthalene

Chemical name Naphthalene

Other names Tar Camphor, White Tar, Moth Flakes

Chemical formula $C_{10}H_8$

SMILES C1(C=CC=C2)=C2C=CC=C1

Molar mass 128.17052 g/mol

Appearance White solid crystals/flakes, strong odor of coal tar

CAS number 91-20-3

Properties

Density 1.14 g/cm^3

Solubility in water Insoluble in water

Melting point 80.5 °C

Boiling point 218 °C

Hazards

MSDS External MSDS

Main hazards Flammable, sensitizer, possible carcinogen. Dust can form explosive mixtures with air

Flash point 79 - 87 °C

Autoignition temperature 525 °C

R/S statement R: 20, 21, 22, 36, 37, 38, 43, 45 S: 16, 26, 36, 37, 39, 45

RTECS number QJ0525000

Except where noted otherwise, data are given for materials in their standard state (at 25°C, 100 kPa)

Naphthalene (not to be confused with naphtha) (also known as *naphthalin*, *naphthaline*, *tar camphor*, *white tar*, *albocarbon*, or *naphthene*), is a crystalline, aromatic, white, solid hydrocarbon, best known as the primary ingredient of mothballs. Naphthalene is volatile, forming a flammable vapor. Its molecules consist of two fused benzene rings. It is manufactured from coal tar, and converted to phthalic anhydride for the manufacture of plastics, dyes and solvents. It is also used as an antiseptic and insecticide, especially in mothballs. p-Dichlorobenzene is now often used instead of naphthalene as a mothball substitute. Naphthalene easily sublimates at room temperature.

History

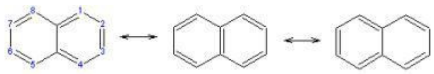
In 1819-1820, at least two chemists reported a white solid with a pungent odor derived from the distillation of coal tar. In 1821, John Kidd described many of this substance's properties and the means of its production, and proposed the name naphthaline, as it had been derived from a kind of naphtha (a broad term encompassing any volatile, flammable liquid hydrocarbon mixture, including coal tar).

Naphthaline's empirical formula, C_5H_4, was determined by Michael Faraday in 1826. The structure of two fused benzene rings was proposed by Emil Erlenmeyer in 1866, and confirmed by Carl Graebe three years later.

Structure and reactivity

A naphthalene molecule is composed of two fused benzene rings. (In organic chemistry, rings are fused if they share two or more atoms). Accordingly, naphthalene is classified as a benzenoid polycyclic aromatic hydrocarbon (PAH). Naphthalene has three resonance structures, which are shown in the drawing below. Naphthalene has two sets of equivalent hydrogens. The alpha positions are positions 1, 4, 5, and 8 on the drawing below. The beta positions are positions 2, 3, 6, and 7.

Unlike benzene, the carbon-carbon bonds in naphthalene are not of the same length. The bonds C1–C2, C3–C4, C5–C6 and C7–C8 are about 1.36 Å (136 pm) in length, whereas all the other carbon-carbon bonds are about 1.42 Å (142 pm) in length. This has been verified by x-ray diffraction and can be expected from the resonance structures, where the bonds C1–C2, C3–C4, C5–C6 and C7–C8 are double in two of the three structures, whereas all the others are double in only one.



Like benzene,naphthalene can undergo electrophilic aromatic substitution. For many electrophilic aromatic substitution reactions, naphthalene is more reactive than benzene, and reacts under milder conditions than does benzene. For example, while both benzene and naphthalene react with chlorine in the presenece of a ferric chloride or aluminium chloride catalyst, naphthalene and chlorine can react to form 1-chloronaphthalene even without a catalyst. Similarly, while both benzene and naphthalene can be alkylated using Friedel-Crafts reactions, naphthalene can also be alkylated by reaction with alkenes or alcohols, with sulfuric or phosphoric acid as the catalyst.

Mono-substitution of naphthalene has two possible isomeric products, corresponding to substitution at an alpha or beta position, respectively. Usually, the major product has the electrophile in the alpha position. The selectivity for alpha over beta substitution can be rationalized in terms of the resonance structures of the intermediate: for the alpha substitution intermediate, seven resonance structures can be drawn, of which four preserve an aromatic ring. For beta substitution, the intermediate has only six resonance structures, and only two of these are aromatic. Sulfonation, however, gives a mixture of the "alpha" product 1-naphthalenesulfonic acid and the "beta" product 2-naphthalenesulfonic acid, with the ratio dependent on reaction conditions.

Naphthalene can be hydrogenated under high pressure or with a suitable catalyst to give 1,2,3,4-tetrahydronaphthalene, a solvent sold under the trade name Tetralin. Further hydrogenation yields decahydronaphthalene or Decalin (C10H18, also known as bicyclo[4.4.0]decane). Oxidation of naphthalene with chromate or permanganate, or catalytic oxidation with O2 and a vanadium catalyst, gives phthalic acid.

Production

Most naphthalene is derived from coal tar. From the 1960s until the 1990s, significant amounts of naphthalene were also produced from heavy petroleum fractions during petroleum refining, but today petroleum-derived naphthalene represents only a minor component of naphthalene production.

Naphthalene is the most abundant single component of coal tar. While the composition of coal tar varies with the coal from which it is produced, typical coal tar is about 10% naphthalene by weight. In industrial practice, distillation of coal tar yields an oil containing about 50% naphthalene, along with a variety of other aromatic compounds. This oil, after being washed with aqueous sodium hydroxide to remove acidic components, chiefly various phenols, and with sulfuric acid to remove basic components, is fractionally distilled to isolate naphthalene. The crude naphthalene resulting from this process is about 95% naphthalene by weight. The chief impurity is the sulfur-containing aromatic compound thionaphthene. Petroleum-derived naphthalene is usually purer than that derived from coal tar. Where purer naphthalene is required, crude naphthalene can be further purified by recrystallizing it from any of a variety of solvents.

Incidence in nature

Trace amounts of naphthalene are produced by magnolias and specific types of deer. Naphthalene has also been found in the Formosan subterranean termite, possibly as a repellant against "ants, poisonous fungi and nematode worms."

Uses

Naphthalene's most familiar use is as a household fumigant, such as in mothballs. In a sealed container containing naphthalene pellets, naphthalene vapors build up to levels toxic to both the adult and larval forms of many moths that are destructive to textiles. Other fumigant uses of naphthalene include use in soil as a fumigant pesticide, and in attic spaces to repel animals.

In the past, naphthalene was administered orally to kill parasitic worms in livestock.

Larger volumes of naphthalene are used as a chemical intermediate to produce other chemicals. The single largest use of naphthalene is the industrial production of phthalic anhydride, although more phthalic anhydride is made from o-xylene than from naphthalene. Other naphthalene-derived chemicals include alkyl naphthalene sulfonate surfactants, and the insecticide carbaryl. Naphthalenes substituted with combinations of strongly electron-donating functional groups, such as alcohols and amines, and strongly electron-withdrawing groups, especially sulfonic acids, are intermediates in the preparation of many synthetic dyes. The hydrogenated naphthalenes tetrahydronaphthalene (Tetralin) and decahydronaphthalene (Decalin) are used as low-volatility solvents.

Health effects

In humans, exposure to large amounts of naphthalene may damage or destroy red blood cells. This could cause the body to have too few red blood cells until it replaces the destroyed cells. Humans, particularly children, have developed this condition after ingesting mothballs or deodorant blocks containing naphthalene. Some of the symptoms of this condition are fatigue, lack of appetite, restlessness, and pale skin. Exposure to large amounts of naphthalene may also cause nausea, vomiting, diarrhea, blood in the urine, and jaundice (yellow coloration of the skin).

When the U.S. National Toxicology Program exposed male and female rats and mice to naphthalene vapors on weekdays for two years (1), male and female rats exhibited: evidence of carcinogenic activity, based on increased incidences of adenoma and neuroblastoma of the nose, female mice exhibited some evidence of carcinogenic activity, based on increased incidences of alveolar and bronchiolar adenomas of the lung, and male mice exhibited no evidence of carcinogenic activity.

The International Agency for Research on cancer (IARC) (2) classifies naphthalene as possibly carcinogenic to humans [Group 2B]. It also points out that acute exposure causes cataracts in humans, rats, rabbits, and mice and, that haemolytic anaemia, described above, can occur in children and infants after oral or inhalation exposure or after maternal exposure during pregnancy.

Over 400 million people have an inherited condition called glucose-6-phosphate dehydrogenase deficiency. For these people, exposure to naphthalene is harmful and may cause hemolytic anemia, which causes their erythrocytes to break down.

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Natron

Natron is a non-radioactive compound composed of the basic elements sodium, hydrogen, carbon, and oxygen. Some sources say that a simple mixture can be made with sodium bicarbonate, which is commonly known as baking soda, and sodium chloride, which is salt. Its color can vary from white, gray, yellow or it can even be colorless. The molecular weight is 286.14 gm. Natron's empirical formula is

Na***2***(CO***3***)x10(H***2***O) and its chemical formula is Na2CO3x10(H2O). Natron can be found in saline lake beds in arid environments. The name natron is Latin in origin meaning “Soda.” The density can range from 1.42- 1.47.

Uses for Natron

One common use was in ancient Egypt as a part of mummification. The mineral works as a drying agent, drawing the water out of the body. At the same time the bicarbonate, when subjected to moisture, increases the pH and creates a hostile environment for bacteria. Natron was also thought to promote spiritual safety for both the living and the dead. It was also added to castor oil to produce a smokeless fuel which allowed Egyptian artisans to paint

elaborate artworks inside ancient tombs without them becoming besmirched with soot. Natron has also been known to be used as a cleansing product for the home as well as the body which includes the teeth and was used as an early mouthwash. It has also been linked to early antiseptics if placed on wounds and minor cuts. It was also used to rid a house of vermin. Natron is also an ingredient in the making of the distinct color "Egyptian blue." Natron was used to make ceramics and glass as well as to solder precious metals together. If natron was mixed with salt, it could be used to preserve fish and meat. It could also be mixed with oil and it became an early form of soap. Natron was commonly used in glass-making, by the Romans and others, until trade declined after 640 AD.

Natron is used to make Bavarian pretzels. The dough is dipped into a natron solution to give it its brown color and distinctive flavor when baked.

Locations

Natron can be found in the following locations: Quebec, Canada (Rouville Co. and Mont Saint-Hilaire)

Wadi Natrum, Egypt

Showa Province, Ethiopia

Bács-Kiskun Co., Hungary (Great Hungarian Plain)

Szabolcs-Szatmár-Bereg Co., Hungary (Great Hungarian Plain)

Campania, Italy (Naples Province and Somma-Vesuvius Complex)

Northern Region of Russia (Murmanskaja Oblast', Kola Peninsula, Khibiny Massif, Lovozero Massif, Alluaiv Mt, Umbozero Mine, and Kedykverpakhk Mt)

England, UK (Cornwall, St Just District, Botallack - Pendeen Area, Botallack, and Botallack Mine)

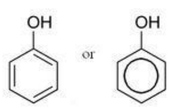
California, USA (Inyo Co.)

Nevada, USA (Churchill Co., Soda Lake District, Humboldt Co., and Mineral Co.)

Oregon, USA (Lake Co.)

Washington, USA (Okanogan Co.)

Phenol



Systematic name Phenol

Other names Carbolic Acid, Benzenol, Phenylic Acid, Hydroxybenzene

Chemical formula C_6H_5OH

SMILES OC1=CC=CC=C1

Molar mass 94.11 g/mol

Appearance White Crystalline Solid

CAS number [108-95-2]

Properties

Density 1.07 g/cm3

Solubility in water 8.3 g/100 ml (20 °C)

Melting point 40.5 °C

Boiling point 181.7 °C

Acidity (p*K**a*) 9.95

Structure

Molecular shape planar

Hazards

MSDS External MSDS

EU classification

Toxic (*T*)

Muta. Cat. 3

Corrosive (*C*)

R-phrases ***R23/24/25*, *R34*, *R48/23/24/25*, *R68***

S-phrases **S1/2, S24/25, S26, S28, S36/37/39, S45**

Flash point 79 °C

Autoignition temperature 715 °C

RTECS number SJ3325000

Related compounds

Related compounds Benzenethiol

Phenol, also known under an older name of *carbolic acid*, is a colourless crystalline solid with a typical sweet tarry odor. Its chemical formula is C6H5OH and its structure is that of a hydroxyl group (-OH) bonded to a phenyl ring; it is thus an aromatic compound.

Phenols

The word phenol is also used to refer to any compound which contains a six-membered aromatic ring, bonded directly to a hydroxyl group (-OH). In effect, phenols are a class of organic compounds of which the phenol discussed in this article is the simplest member.

Properties

Phenol has a limited solubility in water (8.3 g/100 ml). It is slightly acidic: the phenol molecule has weak tendencies to lose the H+ ion from the hydroxyl group, resulting in the highly water-soluble phenoxide anion C6H5O. Compared to aliphatic alcohols, phenol shows much higher acidity,it even reacts with NaOH to lose H+ which aliphatic alcohols do not. This

is due to orbital overlap between the oxygen's lone pairs and the aromatic system, which delocalizes the negative charge throughout the ring and stabilizes the anion. This effect is attenuated, however, due to oxygen's relatively high electronegativity. [1]

Production

Phenol can be made from the partial oxidation of benzene or benzoic acid, by the cumene process, or by the Raschig process. It can also be found as a product of coal oxidation.

Uses

Phenol has antiseptic properties, and was used by Sir Joseph Lister in his pioneering technique of antiseptic surgery, though the skin irritation caused by continual exposure to phenol eventually led to the substitution of aseptic (germ-free) techniques in surgery. It is one of the main components of the commercial antiseptic TCP (trichlorophenol).

Phenol has anesthetic properties, and is the active ingredient in some oral anesthetics such as Chloraseptic spray.

It is also used in the production of drugs (it is the starting material in the industrial production of aspirin), weedkiller, and synthetic resins (Bakelite, one of the first synthetic resins to be manufactured, is a polymer of phenol with formaldehyde). Exposure of the skin to concentrated phenol solutions causes chemical burns which may be severe; in laboratories where it is used, it is usually recommended that polyethylene glycol solution is kept available for washing off splashes. Washing with large amounts of plain water (most labs have a safety shower or eye-wash) and removal of contaminated clothing are required, and immediate ER treatment for large splashes; particularly if the phenol is mixed with chloroform (a commonly used mixture in molecular biology for DNA purification). Notwithstanding the effects of concentrated solutions, it is also used in cosmetic surgery as an exfoliant, to remove layers of dead skin. It is also used in phenolization, a surgical procedure used to treat an ingrown nail, in which it is applied to the toe to prevent regrowth of nails.

Injections of phenol have occasionally been used as a means of rapid execution.

Phenol was also used as a means of extermination by the Nazis during the Second World War. Phenol injections were given to thousands of people in concentration camps, especially at Auschwitz-Birkenau. Injections were administered either by medical doctors or by their assistants; such injections were originally given intravenously, more commonly in the arm, but injection directly into the heart, so as to induce nearly instant death, was later preferred. [2]

Phenols are extremely harmful to cats. [3]

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2. ^ Killing through phenol injection. Auschwitz - FINAL STATION EXTERMINATION. Johannes Kepler University, Linz, Austria. Retrieved on 2006-09-29.
3. ^ Poison - hidden dangers?. Information for cat owners. Feline Advisory Bureau. Retrieved on 2006-09-29.

Salicylic acid

Chemical name 2-Hydroxybenzoic acid

Chemical formula $C_7H_6O_3$

Molecular mass 138.12 g/mol

Melting point 159 °C

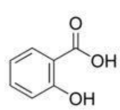
Boiling point 211 °C (2666 Pa)

Density 1.44 g/cm^3 (at 20 °C)

pKa 2.97

CAS number [69-72-7]

SMILES c1(O)ccccc1C(O)=O



Disclaimer and references

Salicylic acid is the chemical compound with the formula $C_6H_4(OH)CO_2H$, where the OH group is adjacent to the carboxylic acid group. This colorless crystalline organic acid is widely used in organic synthesis and functions as a plant hormone. It is probably best known as a compound that is chemically similar but not identical to the active component of aspirin. The name derives from the latin word for the willow tree (Salix), from whose bark it can be obtained.

Medicinal and cosmetic uses

Also known as beta hydroxy acid (compare to AHA), salicylic acid is the key additive in many skin-care products for the treatment of acne, psoriasis, callouses, corns, keratosis pilaris and warts. It treats acne by causing skin cells to slough off more readily, preventing

pores from clogging up. This effect on skin cells also makes salicylic acid an active ingredient in several shampoos meant to treat dandruff. Use of straight salicylic solution may cause hyperpigmentation on unpretreated skin for those with darker skin types (Fitzpatrick phototypes IV, V, VI), as well as with the lack of use of a broad spectrum sunblock.[1][2]

The medicinal properties of salicylate (mainly for fever relief) have been known since ancient times. The substance occurs in the bark of willow trees; the name salicylic acid is derived from salix, the Latin name for the willow tree. [3]

Aspirin (acetylsalicylic acid or ASA) can be prepared by the esterification of the phenolic hydroxyl group of salicylic acid.

Subsalicylate in combination with bismuth form the popular stomach relief aid known commonly as Pepto-Bismol. When combined, the two key ingredients help control diarrhea, nausea, heartburn, and gas. It is also a very mild anti-biotic.

Toxicological effects of 100% salicylic acid, however, are mostly harmful. It is harmful by ingestion, inhalation, and through skin absorption. It acts as an irritant, and chronic effects have shown 100% salicylic acid to cause DNA damage, and also cause allergic reactions after repeated exposure. This is why most acne treatment medications use a percent range of 2-5 in solution.

Other uses

- Salicylic acid is toxic if ingested in large quantities, but in small quantities is used as a food preservative and antiseptic in toothpaste. For some people with salicylate sensitivity even these small doses can be harmful.

See also

- Phenol
- Aspirin

Footnotes

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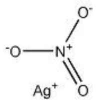
Silver nitrate



Molecular formula $AgNO_3$

Molar mass 169.8731 g/mol

Appearance white solid

CAS number [7761-88-8]

Properties

Density and phase 4.35 g/cm**3**, solid

Solubility in water 219 g/100 ml (20 °C °C)

Melting point 212 °C

Boiling point 444 °C decomp.

Structure

Coordination geometry Trigonal Pyramidal

Crystal structure rhombohedral

Hazards

MSDS External MSDS

EU classification

Corrosive (*C*)
Dangerous for
the environment (*N*)
R-phrases **R34**, **R50/53**

S-phrases **S1/2**, **S26**, **S45**, **S60**, **S61**

Flash point non-flammable

Related compounds

Other cations Copper(II) nitrate

Except where noted otherwise, data are given for materials in their standard state (at 25 °C, 100 kPa)

Silver nitrate is a chemical compound with chemical formula $AgNO_3$. This nitrate of silver is a light-sensitive ingredient in photographic film and is a poisonous, corrosive compound. Silver nitrate crystals can be produced by dissolving silver in nitric acid and evaporating the solution. The compound notably stains skin a greyish or black color that is made visible after exposure to sunlight.

When making photographic film, silver nitrate is reacted with halide salts of sodium or potassium to form insoluble silver halide in situ in photographic gelatin, which is then applied to strips of tri-acetate or polyester. Photons from sunlight, X-rays or other sources, initiate a chemical chain reaction: when photons strike silver nitrate molecules, they free electrons from the halide ions. These free electrons roam through the crystal and settle in structural imperfections called sensitivity specks. These specks attract positive silver ions, which are then neutralized to form groups of stable silver atoms, creating a latent image that is chemically developed to reveal a photographic image.

Silver nitrate has antiseptic properties. It is sometimes dropped into newborn babies' eyes at birth to prevent contraction of gonorrhoea or chlamydia from the mother. Disposal of even small quantities of silver nitrate in toilets connected to a septic tank is guaranteed to destroy the septic bacteria and necessitate pumping out and flushing and seeding with fresh bacteria.

Fused silver nitrate, shaped into sticks, was traditionally called *lunar caustic*. It is used as a cauterizing agent.

In histology, silver nitrate is used for silver staining, for demonstrating proteins and nucleic acids. For this reason it is also used to demonstrate proteins in PAGE gels. It is also used as a stain in scanning electron microscopy.

Silver nitrate is used to prepare some silver-based explosives, such as the fulminate, azide, or acetylide, through a precipitation reaction.

Silver nitrate may be used to electroplate metals if dissolved in water.

Sodium chloride

Systematic name Sodium chloride

Other names Common salt, halite, table salt

Molecular formula NaCl

Molar mass 58.442 g/mol

Appearance White or colourless, solid or liquid

CAS number [7647-14-5]

Properties

Density and phase 2.16 g/cm^3, solid

Solubility in water 35.9 g/100 ml (25 °C)

Melting point 801 °C (1074 K)

Boiling point 1465 °C (1738 K)

Structure

Coordination geometry Octahedral

Crystal structure Face centered cubic

Hazards

MSDS External MSDS

Main hazards Irritant and Might Sting
Flash point Non-flammable

R/S statement R: none, S: none

RTECS number VZ4725000

Related compounds

Other anions NaF, NaBr, NaI

Other cations LiCl, KCl, RbCl, CsCl, MgCl2, CaCl2

Related salts Sodium acetate

Except where noted otherwise, data are given for materials in their standard state (at 25 °C, 100 kPa)

Sodium chloride, also known as *common salt*, *table salt*, or halite, is a chemical compound with the formula NaCl. Sodium chloride is the salt most responsible for the salinity of the ocean and of the extracellular fluid of many multicellular organisms. As the main ingredient in edible salt, it is commonly used as a condiment and food preservative.

Crystal structure

Sodium chloride forms crystals with cubic symmetry. In these, the larger chloride ions, shown to the left as green spheres, are arranged in a cubic close-packing, while the smaller sodium ions, shown to the left as blue spheres, fill the octahedral gaps between them.

Each ion is surrounded by six of the other kind. This same basic structure is found in many other minerals, and is known as the halite structure. This arrangement is known as cubic close packed (ccp).

It is held together with an ionic bond and electrostatic forces.

Biological importance

Sodium chloride is essential to life on Earth. Most biological tissues and body fluids contain a varying amount of salt.

Salt throughout history

Salt's preservative ability was a foundation of civilization. It eliminated dependency on the seasonal availability of food and allowed travel over long distances. By the Middle Ages, caravans consisting of as many as forty thousand camels traversed four hundred miles of the Sahara bearing salt, sometimes trading it for slaves.

During his protests in India, Gandhi performed the famous salt march to challenge the British-imposed monopoly on salt.

In religion

There are thirty-five references (verses) to salt in the Bible (King James Version), the most familiar probably being the story of Lot's wife, who was turned into a pillar of salt when she disobeyed the angels and looked back at the wicked city of Sodom (Genesis 19:26). In the Sermon on the Mount, Jesus also referred to his followers as the salt of the earth, a reference to salt's great value in the ancient world. Most of the time when talking about salt, the Bible is speaking of wisdom or age and wisdom combined.

In the native Japanese religion shinto, salt is seen as "corrupt" and can be used to purify (bless) locations and people, such as in Sumo Wrestling.

Production and use

Nowadays, salt is produced by evaporation of seawater or brine from other sources, such as brine wells and salt lakes, and by mining *rock salt*, called halite.

While most people are familiar with the many uses of salt in cooking, they might be unaware that salt is used in a plethora of applications, from manufacturing pulp and paper to setting dyes in textiles and fabric, to producing soaps and detergents. In most of Canada and the northern USA, large quantities of rock salt are used to help clear highways of ice during winter, although "Road Salt" loses its melting ability at temperatures below -15°C to -20°C (5°F to -4°F).

Synthetic Uses

Salt is also the raw material used to produce chlorine which itself is required for the production of many modern materials including PVC and pesticides.

Industrially, elemental chlorine is usually produced by the electrolysis of sodium chloride dissolved in water. Along with chlorine, this chloralkali process yields hydrogen gas and sodium hydroxide, according to the chemical equation

2 NaCl + 2 H2O ’ Cl2 + H2 + 2 NaOH

Sodium metal is produced commercially through the electrolysis of liquid sodium chloride. This is done in a Down's cell in which the NaCl is mixed with calcium chloride to lower the melting point below 700 °C. As calcium is more electropositive than sodium, no calcium will be formed at the cathode. This method is less expensive than the previous method of electrolyzing sodium hydroxide.

Solubility of NaCl in various solvents (g NaCl / 100 g of solvent at 25 C)

H***2***O 36

Liquid ammonia 3.02

Methanol 1.4

Formic acid 5.2

Sulfolane 0.005

Acetonitrile 0.0003

Acetone 0.000042

Formamide 9.4

Dimethylformamide 0.04

Reference: Burgess, J. Metal Ions in Solution (Ellis Horwood, New York, 1978) ISBN 0-85312-027-7

Flavour enhancer

Main article: Edible salt

Salt is commonly used as a flavour enhancer for food and has been identified as one of the basic tastes. Unfortunately, given its history, this has resulted in large sections of the developed world ingesting salt massively in excess of the required intake, particularly in colder climates where the required intake is much lower. This causes elevated levels of blood

pressure (hypertension) in some, which in turn is associated with increased risks of heart attack and stroke. Consuming salt in excess can also dehydrate the human body.

Biological uses

Many microorganisms cannot live in an overly salty environment: water is drawn out of their cells by osmosis. For this reason salt is used to preserve some foods, such as smoked bacon or fish. It has also been used to disinfect wounds. In medieval times salt would be rubbed into household surfaces as a cleansing agent.

De-icing

While salt was a scarce commodity in history, industrialized production has now made salt plentiful. About 51% of world output is now used by cold countries to de-ice roads in winter, see Grit bin. This works because salt and water form a eutectic mixture that has about a 10°C lower freezing point than pure water (see Freezing-point depression): the ions prevent regular ice crystals from forming (below 10°C salt will not prevent water from freezing). Concerns are arising that this use may be harmful to the environment though, and, in Canada, norms were developed to minimize the use of salt in de-icing.

Additives

The salt sold for consumption today is not pure sodium chloride. In 1911 Magnesium carbonate was first added to salt to make it flow more freely. In 1924 trace amounts of iodine in form of sodium iodide, potassium iodide or potassium iodate were first added, creating iodized salt to reduce the incidence of simple goiter.

Other facts

- Salty soil is generally unfit for agriculture, hence the practice of salting the earth.
- Due to its high concentration of salt, the Dead Sea has such a high density that some objects which are not normally buoyant can float on its surface. Humans float easily, having a density slightly less than that of pure water. (Only 8% of the salt in the Dead Sea is sodium chloride; 53% is magnesium chloride, 37% is potassium chloride.)
- The cities of Cincinnati, Detroit and Hutchinson, Kansas are on top of active salt mines.
- The Third Reich stored vast amounts of money, paintings and artworks in salt mines, and many important documents and items continue to be stored in former salt mines to this day. Salt mines are also used to store nuclear waste.

See also

- Edible salt

Sodium hypochlorite

Other names Sodium chlorate(I)

Molecular formula NaClO

Molar mass 74.44 g/mol

Appearance white solid

CAS number [7681-52-9]

Properties

Density and phase 1.07-1.14 g/cm^3 liquid

Solubility in water Fully miscible

Melting point 18°C Pentahydrate

Boiling point 101°C Decomposes

Hazards

EU classification

Corrosive (*C*)
Dangerous for
the environment (*N*)

R-phrases R31, R34, R50

S-phrases S1/2, S28, S45, S50, S61

Related compounds

Other anions

Sodium chloride
Sodium chlorite
Sodium chlorate
Sodium perchlorate

Other cations

Lithium hypochlorite
Calcium hypochlorite

Related compounds Hypochlorous acid

Except where noted otherwise, data are given for materials in their standard state (at 25 °C, 100 kPa)

Sodium hypochlorite is a chemical compound with the formula NaClO. A solution of sodium hypochlorite is frequently used as a disinfectant and as a bleaching agent; indeed, often it is simply called "bleach", though other chemicals are sometimes given that name as well.

Production

Sodium hypochlorite may be prepared by absorbing chlorine gas in cold sodium hydroxide solution:

$2NaOH + Cl_2 \rightarrow NaCl + NaClO + H_2O$

Sodium hydroxide and chlorine are commercially produced by the chloralkali process, and there is no need to isolate them to prepare sodium hypochlorite. Hence NaClO is prepared industrially by the electrolysis of sodium chloride solution without any separation between the anode and the cathode. The solution must be kept below 40 °C (by cooling coils) to prevent the formation of sodium chlorate.

The commercial solutions always contain significant amounts of sodium chloride (common salt) as the main byproduct, as seen in the equation above.

Packaging and sale

Household bleach sold for use in laundering clothes is a 3-6% solution of sodium hypochlorite at the time of manufacture. Strength varies from one formulation to another and gradually decreases with long storage.

A 12% solution is widely used in waterworks for the chlorination of water. High-test hypochlorite (HTH) is sold for chlorination of swimming pools and contains approximately 30% sodium hypochlorite. The crystalline salt is also sold for the same use; this salt usually contains less than 50% of sodium hypochlorite. However, the level of "active chlorine" may be much higher.

Uses

In household bleach form, sodium hypochlorite is used for removal of stains from laundry. It is particularly effective on cotton fiber, which stains easily but bleaches well. 50 to 250 ml per load is usually recommended for a standard-size washer. Hot water increases

the activity of the bleach, owing to the thermal decomposition of hypochlorite which ultimately generates environmentally-undesirable chlorate.

A weak solution of 1% household bleach in warm water is used to sanitize smooth surfaces prior to brewing of beer or wine. Surfaces must be rinsed to avoid imparting flavors to the brew; these chlorinated byproducts of sanitizing surfaces are also harmful.

A 1 in 5 dilution of household bleach with water (1 part bleach to 4 parts water) is effective against many bacteria and some viruses, and is often the disinfectant of choice in cleaning surfaces in hospitals (Primarily in the United States). The solution is corrosive, and needs to be thoroughly removed afterwards, so the bleach disinfection is sometimes followed by an ethanol disinfection.

For shock chlorination of wells or water systems, a 2% solution of household bleach is used. For larger systems, HTH is more practical because lower rates can be used. The alkalinity of the sodium hypochlorite solution also causes the precipitation of minerals such as calcium carbonate, so that the shock chlorination is often accompanied by a clogging effect. The precipitate also preserves bacteria, making this practice somewhat less effective.

Sodium hypochlorite has been used for the disinfection of drinking water, at a concentration equivalent to about 1 liter of household bleach per 4000 liters of water is used. The exact amount required depends on the water chemistry, temperature, contact time, and presence or absence of sediment. In large-scale applications, residual chlorine is measured to titrate the proper dosing rate. For emergency disinfection, the US EPA recommends the use of 2 drops of 5%ac household bleach per quart of water. If the treated water doesn't smell of bleach, 2 more drops are to be added.

The use of chlorine-based disinfectants in domestic water, although widespread, has led to some controversy due to the formation of small quantities of harmful byproducts such as chloroform.

It is also used in dentistry, during root canal treatment, disinfecting the canal and dissolving any remaining pulp tissue. Historically, Henry Drysdale Dakin's solution (0.5%) had been used. Nowadays, 2.5-5.25% solutions are being used.

An alkaline solution (pH 11.0) of sodium hypochlorite is used to treat dilute (< 1 g/L) cyanide wastewater, e.g. rinsewater from an electroplating shop. In batch treatment operations, sodium hypochlorite has been used to treat more concentrated cyanide wastes, such as silver cyanide plating solutions. A well-mixed solution is fully treated when an excess of chlorine is detected.

Mechanism of action

Like all hypochlorites, sodium hypochlorite is a salt of hypochlorous acid, HClO. Sodium hypochlorite solution is a light yellow green transparent liquid. In water, it partially splits into the sodium cation Na+ and the hypochlorite anion ClO, while a substantial portion hydrolyses into sodium hydroxide and hypochlorous acid. The oxidizing power of the latter and of the hypochlorite anion cause the bleaching effect. The hypochlorite anion's negative charge, however, prevents it from diffusing through the cell walls of bacteria and microbes, making it a poor disinfectant. However, the hypochlorous acid molecules that exist in equilibrium with the hypochlorite anion, due to their neutral charge and small size, easily diffuse through the cell walls of bacteria. This changes the oxidation-reduction potential

(ORP) of the cell, and inactivates the enzyme triosephosphate dehydrogenase. Triosephosphate dehydrogenase (or glyceraldehyde 3-phosphate dehydrogenase/GAPDH) is essential for the digestion of glucose, but is particularly sensitive to oxidizing agents. Its inactivation effectively destroys the micro-organism's ability to function.

Cautions

Sodium hypochlorite is a strong oxidizer. Products of the oxidation reactions are corrosive. Solutions burn skin and cause eye damage, particularly when used in concentrated forms. However, as recognized by the NFPA, only solutions containing more than 40% sodium hypochlorite by weight are considered hazardous oxidizers. Solutions less than 40% are classified as a moderate oxidizing hazard (NFPA 430, 2000).

Household bleach and pool chlorinator solutions are typically stabilized by a significant concentration of lye (caustic soda, NaOH) as part of the manufacturing reaction. Skin contact will produce caustic irritation or burns due to defatting and saponification of skin oils and destruction of tissue. The slippery feel of bleach on skin is due to this process.

Sodium thiosulfate (hypo) is an effective chlorine neutralizer. Rinsing with a 5mg/L solution, followed by washing with soap and water, quickly removes chlorine odor from the hands.

Chlorination of drinking water can oxidize organic contaminants, producing trihalomethanes (also called haloforms), which are carcinogenic. The extent of the hazard thus created is a subject of disagreement.

Mixing bleach with some household cleaners can be hazardous. For example, mixing an acid cleaner with sodium hypochlorite bleach generates chlorine gas. Mixing with ammonia solutions produces chloramines. Both chlorine gas and chloramine gas are toxic. Bleach can react violently with hydrogen peroxide and produce oxygen gas:

$H_2O_2 + NaClO$ ’ $NaCl + H_2O + O_2$

It is estimated that there are about 3300 accidents needing hospital treatment caused by sodium hypochlorite solutions each year in British homes (RoSPA, 2002).

Bibliography

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Antivirals

Antiviral drugs are a class of medication used specifically for treating viral infections. Like antibiotics, specific antivirals are used for specific viruses. Antiviral drugs are one class of antimicrobials, a larger group which also includes antibiotics, anti-fungal and anti-parasitic drugs. They are relatively harmless to the host, and therefore can be used to treat infections. They should be distinguished from viricides, which actively deactivate virus particles outside the body.

Most of the antivirals now available are designed to help deal with HIV, herpesvirus, which is best known for causing cold sores but actually covers a wide range of diseases, and the hepatitis B and C viruses, which can cause liver cancer. Researchers are now working to extend the range of antivirals to other families of pathogens.

The emergence of antivirals is the product of a greatly expanded knowledge of the genetic and molecular function of organisms, allowing biomedical researchers to understand the structure and function of viruses, major advances in the techniques for finding new drugs, and the intense pressure placed on the medical profession to deal with the human immunodeficiency virus (HIV), the cause of the deadly acquired immunodeficiency syndrome (AIDS) epidemic. Though no one could sensibly claim that AIDS has been a benefit to humankind, it has certainly done much to advance the state of antiviral technology.

History

Modern medical science and practice has something of an armory of effective tools, ranging from antiseptics and anesthetics to vaccines and antibiotics. One field in which medicine has been traditionally weak, however, is in finding drugs to deal with viral infections. To be sure, highly effective vaccines have been developed to prevent such diseases, but traditionally, once somebody came down sick with a virus, there was little that could be done but recommend rest and plenty of fluids until the disease ran its course.

The first experimental antivirals were developed in the 1960s, mostly to deal with herpesviruses, and were found using traditional trial-and-error drug discovery methods.

Since the mid-1980s, that scenario has changed dramatically. Dozens of antiviral treatments are now available, and most medical researchers feel we are only scratching at the surface of what can be done with these new drugs.

Development of antiviral drugs

Viruses, not quite proper living things, consist of a genome and sometimes a few enzymes (biocatalysts) stored in a capsule made of protein, and very rarely covered with a lipid (fat) layer. Viruses cannot reproduce on their own, and so they propagate by hijacking cells to do the job for them.

To develop early antivirals, researchers grew cultures of cells and infected them with the target virus. They then introduced chemicals into the cultures thought likely to inhibit viral activity, and observed whether the level of virus in the cultures rose or fell. Chemicals that seemed to have an effect were selected for closer study.

This was a very time-consuming, hit-or-miss procedure, and in the absence of a good knowledge of how the target virus worked, not very good at discovering antivirals that were effective and had few side effects. It wasn't until the 1980s, when the full genetic sequences of viruses began to be unraveled, that researchers began to learn how viruses worked in detail, and exactly what kinds of molecules were needed to jam their machinery.

The general idea behind modern antiviral drug design is to identify viral proteins, or parts of proteins, that can be disabled. These "targets" should generally be as unlike any proteins or parts of proteins in humans as possible, to reduce the likelihood of side effects. The targets should also be common across many strains of a virus, or even among different

species of virus in the same family, so a single drug will have broad effectiveness. For example, a researcher might target a critical enzyme synthesized by the virus, but not the patient, that is common across strains, and see what can be done to interfere with its operation.

Once targets are identified, candidate drugs can be selected, either from drugs already known to have appropriate effects, or by actually designing the candidate at the molecular level with a computer-aided design program.

In either case, the candidates can be synthesized by plugging the gene that synthesizes that protein into bacteria or other kinds of cells. The bacteria or cells are then cultured for mass production of the protein, which can then be sifted by "rapid screening" technologies to see which of the candidates are the most effective.

Antiviral drug design strategies

Researchers working on such "rational drug design" strategies for developing antivirals have tried to attack viruses at every stage of their life cycles. Viral life cycles vary in their precise details depending on the species of virus, but they all share a general pattern:

- Attachment to a host cell.
- Release of viral genes and possibly enzymes into the host cell.
- Replication of viral components using host-cell machinery.
- Assembly of viral components into complete viral particles.
- Release of viral particles to infect new host cells.

The best time to attack a virus is as early as possible in its life cycle. In a sense, this is exactly what vaccines do. Vaccines traditionally consist of a weakened or killed version of a pathogen, though more recently "subunit" vaccines have been devised that consist strictly of protein targets from the pathogen. They stimulate the immune system without doing serious harm to the host, and so when the real pathogen attacks the subject, the immune system responds to it quickly and blocks it.

Vaccines have an excellent track record for effectiveness, but they are of limited use in treating a patient who has already been infected. That's where antiviral drugs come in.

One approach is to interfere with the ability of a virus to get into a target cell. The virus has to take a sequence of actions to do this, beginning with binding to a specific "receptor" molecule on the surface of the host cell and ending with the virus "uncoating" inside the cell and releasing its payload. Viruses that have a lipid envelope must also fuse their envelope with the target cell, or with a vesicle that transports them into the cell, before they can uncoat.

This stage of viral replication can be inhibited in two ways: 1. Using agents which mimic the virus-associated protein (VAP) and bind to the cellular receptors. This may include VAP Anti-idiotypic antibodies, anti-receptor antibodies, and natural ligands of the receptor and anti-receptor antibodies. 2. Using agents which mimic the receptor and bind to the VAP. This includes anti-VAP antibodies, receptor anti-idiotypic antibodies, extraneous receptor and synthetic receptor mimics.

This strategy of designing drug can be very expensive. The process of generating anti-idiotypic antibodies is not fully understood. And it has very poor pharmacokinetics.

A very early stage of viral infection is viral entry, when the virus attaches to and enters the host cell. A number of "entry-inhibiting" or "entry-blocking" drugs are being developed to fight HIV. HIV most heavily targets the immune-system white blood cells known as "helper T cells", and identifies these target cells through T-cell surface receptors designated "CD4" and "CCR5". Attempts to interfere with the binding of HIV with the CD4 receptor have failed to stop HIV from infecting helper T cells, but research continues on trying to interfere with the binding of HIV to the CCR5 receptor in hopes that will be more effective.

However, two entry-blockers, amantadine and rimantadine, have been introduced to combat influenza, and researchers are working on entry-inhibiting drugs to combat hepatitis B and C virus.

One entry-blocker is pleconaril. Pleconaril works against rhinoviruses, which cause the common cold, by blocking a pocket on the surface of the virus that controls the uncoating process. This pocket is similar in most strains of rhinoviruses and enteroviruses, which can cause diarrhea, meningitis, conjunctivitis, and encephalitis.

A second approach is to target the processes that synthesize virus components after a virus invades a cell. One way of doing this is to develop "nucleotide or nucleoside analogues" that look like the building blocks of RNA or DNA, but jam the enzymes that synthesize the RNA or DNA once the analogue is incorporated.

The first successful antiviral, aciclovir, is a nucleoside analogue, and is effective against herpesvirus infections. The first antiviral drug to be approved for treating HIV, zidovudine (AZT), is also a nucleoside analogue.

An improved knowledge of the action of reverse transcriptase has led to better nucleoside analogues to treat HIV infections. One of these drugs, lamivudine, has been approved to treat hepatitis B, which uses reverse transcriptase as part of its replication process. Researchers have gone farther and developed inhibitors that do not look like nucleosides, but can still block reverse transcriptase.

Other targets being considered for HIV antivirals include RNase H, which is a component of reverse transcriptase that splits the synthesized DNA from the original viral RNA; and integrase, which splices the synthesized DNA into the host cell genome.

Once a virus genome becomes operational in a host cell, it then generates messenger RNA (mRNA) molecules that direct the synthesis of viral proteins. Production of mRNA is initiated by proteins known as transcription factors. Several antivirals are now being designed to block attachment of transcription factors to viral DNA.

Genomics has not only helped find targets for many antivirals, it has provided the basis for an entirely new type of drug, based on "antisense" molecules. These are segments of DNA or RNA that are designed as "mirror images" to critical sections of viral genomes, and the binding of these antisense segments to these target sections blocks the operation of those genomes. A phosphorothioate antisense drug named fomivirsen has been introduced, used to treat opportunistic eye infections in AIDS patients caused by cytomegalovirus, and other antisense antivirals are in the works. An antisense structual type that has proven especially valuable in research is Morpholino antisense. Morpholino oligos have been used to experimentally suppress many viral types including caliciviruses, flaviviruses (including WNV , Dengue and HCV), and coronaviruses and are currently in clinical development.

Yet another devious antiviral technique inspired by genomics is a set of drugs based on ribozymes, which are enzymes that will cut apart viral RNA or DNA at selected sites. In the

natural order of things, ribozymes are used as part of the viral manufacturing sequence, but these synthetic ribozymes are designed to cut RNA and DNA at sites that will disable them.

A ribozyme antiviral to deal with hepatitis C is in field testing, and ribozyme antivirals are being developed to deal with HIV. An interesting variation of this idea is the use of genetically modified cells that can produce custom-tailored ribozymes. This is part of a broader effort to create genetically modified cells that can be injected into a host to attack pathogens by generating specialized proteins that block viral replication at various phases of the viral life cycle.

Some viruses include an enzyme known as a protease that cuts apart viral protein chains so they can be assembled into their final configuration. HIV includes a protease, and so considerable research has been performed to find "protease inhibitors" to attack HIV at that phase of its life-cycle. Protease inhibitors became available in the 1990s and have proven effective, though they can have odd side-effects, for example causing fat to build up in unusual places. Improved protease inhibitors are now in development.

The final stage in the life cycle of a virus is the release of completed viruses from the host cell, and this step has also been targeted by antiviral drug developers. Two drugs named zanamivir and oseltamivir that have been recently introduced to treat influenza prevent the release of viral particles by blocking a molecule named neuraminidase that is found on the surface of flu viruses, and also seems to be constant across a wide range of flu strains.

A second category of tactics for fighting viruses involves encouraging the body's immune system to attack them, rather than attacking them directly. Some antivirals of this sort do not focus on a specific pathogen, instead stimulating the immune system to attack a range of pathogens.

One of the best-known of this class of drugs are interferons, which inhibit viral synthesis in infected cells. One form of human interferon named "interferon alpha" is well-established as a treatment for hepatitis B and C, and other interferons are also being investigated as treatments for various diseases.

A more specific approach is to synthesize antibodies, protein molecules that can bind to a pathogen and mark it for attack by other elements of the immune system. Once researchers identify a particular target on the pathogen, they can synthesize quantities of identical "monoclonal" antibodies to link up that target. A monoclonal drug is now being sold to help fight respiratory syncytial virus in babies, and another is being tested as a treatment for hepatitis B.

Examination of the genomes of viruses and comparison with the human genome show that some are devious, generating proteins that mimic those used by the human immune system, confusing the immune-system response. Researchers are now hunting for antivirals that can recognize these intruder proteins and disable them.

All drugs designed to fight pathogens have a common problem: over the long run, the pathogens evolve to acquire resistance to the drugs. This means that no antiviral will ever be a permanent solution. In fact, the structure of an antiviral compound will have to be tweaked as its target pathogen changes.

This is the nature of the game. However, antivirals are now promising to be the biggest innovation in pharmaceuticals since the introduction of antibiotics during the Second World War, and promise to be a major step forward in health care.

See also

- Antiretroviral drug

Antiretroviral drugs

Antiretroviral drugs are medications for the treatment of infection by retroviruses, primarily HIV. Different classes of antiretroviral drugs act at different stages of the HIV life cycle. Combination of several (typically three or four) antiretroviral drugs is known as *Highly Active Anti-Retroviral Therapy* (*HAART*).

Organizations such as the National Institutes of Health (Bethesda, Maryland, USA) recommend offering antiretroviral treatment to all patients with HIV-related symptoms. However, because of the complexity of selecting and following a regimen, the severity of the side effects, and the importance of compliance to prevent viral resistance, such organizations emphasize the importance of involving patients in therapy choices and recommend analyzing the risks and the potential benefits to patients without symptoms.[1]

Classes of antiretroviral drugs

Antiretroviral drugs are broadly classified by the phase of the retrovirus life-cyle that the drug inhibits. There are thus five broad classifications of antiretroviral drugs in development, though only the first three classes currently have licensed examples:

- Reverse transcriptase inhibitors (RTIs) target construction of viral DNA by inhibiting activity of reverse transcriptase. There are two subtypes of RTIs with different mechanisms of action: nucleoside-analogue RTIs are incorporated into the viral RNA leading to chain termination, while non-nucleoside-analogue RTIs distort the binding potential of the reverse transcriptase enzyme.
- Protease inhibitors (PIs) target viral assembly by inhibiting the activity of protease, an enzyme used by HIV to cleave nascent proteins for final assembly of new virons.
- Fusion inhibitors block HIV from fusing with a cell's membrane to enter and infect it.
- Integrase inhibitors inhibit the enzyme integrase, which is responsible for integration of viral DNA into the DNA of the infected cell. There are several integrase inhibitors currently under clinical trial but none are commercially available.
- Entry inhibitors block HIV-1 from the host cell by binding CCR5, a molecule on the viral membrane termed a co-receptor that HIV-1 normally uses for entry into the cell.

Fixed dose combinations

Fixed dose combinations are multiple antiretroviral drugs combined into a single pill.

Synergistic enhancers

Synergistic enhancers usually do not possess any antiretroviral properties alone, but when they are taken concurrently with antiretroviral drugs they enhance the effect of that drug.

Combination therapy

The life cycle of HIV can be as short as about 1.5 days: from viral entry into a cell; through replication, assembly, and release of additional viruses; to infection of other cells. HIV lacks proofreading enzymes to correct errors made when it converts its RNA into DNA via reverse transcription. Its short life cycle and high error rate cause the virus to mutate very rapidly, resulting in a high genetic variability of HIV. Most of the mutations either are inferior to the parent virus (often lacking the ability to reproduce at all) or convey no advantage, but some of them have a natural selection superiority to their parent and can enable them to slip past defenses such as the human immune system and antiretroviral drugs. The more active copies of the virus, the greater the possibility that one resistant to antiretroviral drugs will be made, so antiretroviral combination therapy defends against resistance by suppressing HIV replication as much as possible.

Combinations of antiretrovirals create multiple obstacles to HIV replication to keep the number of offspring low and reduce the possibility of a superior mutation. If a mutation arises that conveys resistance to one of the drugs being taken, the other drugs continue to suppress reproduction of that mutation. With rare exceptions, no individual antiretroviral drug has been demonstrated to suppress an HIV infection for long; these agents must be taken in combinations in order to have a lasting effect. As a result the standard of care is to use combinations of antiretroviral drugs. Combinations usually comprise two nucleoside-analogue RTIs and one non-nucleoside-analogue RTI or protease inhibitor.[2]

Combinations of antiretrovirals are subject to positive and negative synergies, which limits the number of useful combinations. For example, ddI and AZT inhibit each other, so taking them together is less effective than taking either one separately. Other issues further limit some people's treatment options from antiretroviral drug combinations, including their complicated dosing schedules and often severe side effects.

In recent years drug companies have worked together to combine these complex regimens into simpler formulas, termed fixed dose combinations. For instance, two pills containing two or three medications each can be taken twice daily. This greatly increases the ease with which they can be taken, which in turn increases adherence, and thus their effectiveness over long term. Lack of adherence is a primary cause of resistence development in medication-experienced patients. The highly mutanegenic nature of HIV demands 98% adherence to drug cocktails for the drugs to be totally effective (that means missing less than 6 doses per year). Patients able to adhere at this rate and higher can maintain one regimen

for up to a decade without developing resistence. This greatly increases chances of long-term survival, as it leaves more drugs available to the patient for longer periods of time.

Current treatment guidelines

Antiretroviral drug treatment guidelines have changed many times. Early recommendations attempted a "hit hard, hit early" approach. A more conservative approach followed, with a starting point somewhere between 350 and 500 CD4+ T cells/mm^3. The current guidelines use new criteria to consider starting HAART, as described below. However, there remain a range of views on this subject and the decision of whether to commence treatment ultimately rests with the patient and their doctor.

The current guidelines for antiretroviral therapy (ART) from the World Health Organization reflect the 2003 changes to the guidelines and recommend that in resource-limited settings (that is, developing nations), HIV-infected adults and adolescents should start ART when HIV infection has been confirmed and one of the following conditions is present [3]):

- Clinically advanced HIV disease;
- WHO Stage IV HIV disease, irrespective of the CD4 cell count;
- WHO Stage III disease with consideration of using CD4 cell counts less than 350/µl to assist decision making;
- WHO Stage I or II HIV disease with CD4 cell counts less than 200/µl.

The treatment guidelines in the USA are set by the United States Department of Health and Human Services (DHHS). The current guidelines for adults and adolescents were stated on October 6, 2005 [4]:

- All patients with history of an AIDS-defining illness or severe symptoms of HIV infection regardless of CD4+ T cell count receive ART.
- Antiretroviral therapy is also recommended for asymptomatic patients with less than 200 CD4+ T cells/µl.
- Asymptomatic patients with CD4+ T cell counts of 201–350 cells/µl should be offered treatment.
- For asymptomatic patients with CD4+ T cell of greater than 350 cells/µl and plasma HIV RNA greater than 100,000 copies/ml, most experienced clinicians defer therapy but some clinicians may consider initiating treatment.
- Therapy should be deferred for patients with CD4+ T cell counts of greater than 350 cells/µl and plasma HIV RNA less than 100,000 copies/mL.

The preferred initial regimens are[5]:

- efavirenz + zidovudine + lamivudine

efavirenz + tenofovir + emtricitabine
lopinavir boosted with ritonavir + zidovudine + lamivudine
lopinavir boosted with ritonavir + tenofovir + emtricitabine.

In countries with a high rate of baseline resistance, resistance testing is recommended prior to starting treatment; or, if the initiation of treatment is urgent, then a "best guess" treatment regimen should be started which is then modified on the basis of resistance testing. In the UK, there is 11.8% medium to high level resistance at baseline to the

combination of zidovudine + lamivudine + efavirenz, and 6.4% medium to high level resistance to stavudine + lamivudine + nevirapine.[6]

Because HIV disease progression in children is more rapid than in adults, and laboratory parameters are less predictive of risk for disease progression, particularly for young infants, treatment recommendations from the DHHS have been more aggressive in children than in adults, the current guidelines were published November 3, 2005 [7].

In 2005, the Centers for Disease Control and Prevention in the United States recommended a 28-day HIV drug regimen for those who have been exposed to HIV (HIV Postexposure Prophylaxis [PEP])[8]. The drugs have demonstrated effectiveness in preventing the virus nearly 100% of the time in those who received treatment within the initial 24 hours of exposure. The effectiveness falls to 52% of the time in those who are treated within 72 hours; those not treated within the first 72 hours are not recommended candidates for the regimen.

Concerns

There are several concerns about antiretroviral regimens. The drugs can have serious side effects.[9] Regimens can be complicated, requiring patients to take several pills at various times during the day, although treatment regimens have been greatly simplified in recent years. If patients miss doses, drug resistance can develop.[10] Also, anti-retroviral drugs are costly, and the majority of the world's infected individuals do not have access to medications and treatments for HIV and AIDS.

Research to improve current treatments includes decreasing side effects of current drugs, further simplifying drug regimens to improve adherence, and determining the best sequence of regimens to manage drug resistance.

Responses to Treatment in Older Adults

As people age, their bodies aren't able to repair and rebuild damaged cells, organs or tissues as rapidly as those of younger people. Diseases like HIV that attack and destroy the body's defenses can exacerbate this slowing and increase the risk of developing additional medical problems like diabetes and high blood pressure, and more physical limitations than younger adults with HIV. In the early years of the HIV epidemic (before HAART), older adults' health deteriorated more rapidly than that of younger individuals - regardless of CD4 count. Several studies found that older adults had lower CD4 counts at diagnosis, faster progression to an AIDS diagnosis, more opportunistic infections, and a shorter survival rate than younger adults, regardless of when they were first diagnosed with HIV.

Recent studies have found that a person's age doesn't interfere with the ability of HAART to reduce viral load, but there may be differences between younger and older people in how well the immune system responds to treatment. A study published in AIDS (2000) by Roberto Manfredi and Francesco Chiodo examined the effect of HAART on older people (defined as 55 or older) compared to younger people (35 or younger). The study included 21 older people (8 women, 13 men) and 84 younger people (29 women, 55 men). The researchers found that both groups responded to HAART, especially in reducing viral load. However, CD4 counts did not increase as much in the older people relative to the younger

ones. On average, CD4 counts increased from 212 to 289 for older adults after one year of HAART. During the same period, CD4 counts rose from 231 to 345 for younger people.

Some people may have a very low CD4 count even though they have an undetectable viral load. This may be related to decreased activity in the thymus (the gland where CD4 cells are made). A 2001 study in AIDS conducted by researchers in Los Angeles included 80 HIV-positive veterans (13 were over 55 and 67 were younger). Although both groups of veterans showed dramatic reductions in viral load once they were on treatment, the researchers found significant differences in CD4 levels at 3, 9, 15, and 18 months. After one year on HAART, average CD4 counts increased by 50 for the older men, compared to increases of 100 for the younger ones. This difference was not related to baseline HIV viral load, coinfection with hepatitis C, or the race/ethnicity of participants. These studies represent an important first step in understanding how their age may affect older adults' response to HIV treatment, but more studies are needed to understand the long-term effects of age on HAART in older adults.

Limitations of antiretroviral drug therapy

If an HIV infection becomes resistant to standard HAART, there are limited options. One option is to take larger combinations of antiretroviral drugs, an approach known as *mega-HAART* or salvage therapy. Salvage therapy often increases the drugs' side-effects and treatment costs. Another is to take only one or two antiretroviral drugs, specifically ones that induce HIV mutations that diminish the virulence of the infection. The most common resistance mutation to lamivudine (3TC) in particular appears to do this. Thus, 3TC can be somewhat effective even alone and when the virus is resistant to it.

If an HIV infection becomes sufficiently resistant to antiretroviral-drugs, treatment becomes more complicated and prognosis may deteriorate. Treatment options continue to improve as additional new drugs enter clinical trials. However, the limited distribution of many such drugs denies their benefits to patients in the developing world.

Drug holidays (or "structured treatment interruptions"), are intentional discontinuations of antiretroviral drug treatment. Studies of such interruptions attempt to increase the sensitivity of HIV to antiretroviral drugs. The interruptions attempt to change the selection pressure from the drug resistance back toward resistance to the human immune system, thus breeding a more drug-susceptible virus. HIV spends some of its life-cycle in a state where its DNA is entirely integrated into human DNA. Under certain conditions, drug-resistant strains of the virus can remain dormant in this state, since CD4 T-cells also are dormant when not aroused by invading organisms. The resistant strain can then reemerge when antiretroviral drugs are re-introduced.

Intermittent therapy is an experimental approach designed to reduce exposure to antiretroviral drugs in an effort to mitigate side-effects. Intermittent therapy differs from treatment interruptions in that it involves using a much shorter cycle of switching on and off the antiviral drugs. Studies of such approaches include schedules of Week-on, week-off (also known as "wowo") and Five-days-on, two-days-off (also known as "foto"), which skips treatment on weekends. They also seek to determine what kinds of patients are best suited for this approach. However, initial data suggest that intermittent therapy is ineffective and results in drug resistance.

It is still unclear whether suppressing or even eliminating HIV will be adequate to restore normal immune function in the long term, since HIV can damage the ability of the thymus to produce normally diverse T-cells. Also, rapid suppression of HIV and partial restoration of the immune system sometimes produces a dangerous hypersensitivity reaction, immune reconstitution inflammatory syndrome. Research continues in these areas.

Adverse effects

Adverse effects of antiretroviral drugs vary by drug, by ethnicity, and by individual, and by interaction with other drugs, including alcohol. Hypersensitivity to some drugs may also occur in some individuals. The following list is not complete, but includes several of the common adverse effects experienced by patients taking some antiretroviral drugs: [11]

- Abdominal pain

Alopecia
Anemia
Asthenia
Diarrhea
Dizziness (Vertigo)
Fanconi syndrome
Flatulence
Headache
Hepatitis
Hyperbilirubinemia
Hypercholesterolemia (Dyslipidemia, Hyperlipidemia, high cholesterol)
Hyperpigmentation (of nails, palms, or soles)
Ingrown nails
Insomnia
Jaundice
Liver failure
Malaise
Mental confusion
Myalgia
Myalgic Encephalomyelitis (chronic fatigue syndrome)
Myopathy
Nausea
Neutropenia
Nightmares
Oral ulcers
Pancreatitis
Paresthesia (numbness)
Peripheral neuropathy
Rash
Renal failure or insufficiency
Somnolence (drowsiness)
Stevens-Johnson syndrome

Change in taste perception
Vomiting
Xeroderma (dry skin)
Xerostomia (dry mouth)

See also

- Antiviral drug

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Protease inhibitor

Protease inhibitors (PIs) are a class of medication used to treat or prevent infection by viruses, including HIV and Hepatitis C. PIs prevent viral replication by inhibiting the activity of protease, an enzyme used by the viruses to cleave nascent proteins for final assembly of new virons.

Protease inhibitors have been developed or are presently undergoing testing for treating various viruses:

- HIV/AIDS: antiretroviral protease inhibitors (saquinavir, ritonavir, indinavir, nelfinavir etc.)

Hepatitis C: experimental agents: BILN 2061, VX 950.

Given the specificity of the target of these drugs there is the risk, as in antibiotics, of the development of drug-resistant mutated viruses. To reduce this risk it is common to use together different drugs aimed at different targets.

Antiretrovirals

Protease inhibitors were the second class of antiretroviral drugs developed. In all cases, patents remain in force until 2010 or beyond.

Saquinavir Saquinavir has trade names Fortovase® (soft gel capsule) and Invirase® (hard gel capsule).

Ritonavir Ritonavir has the trade name: Norvir®.

Indinavir Indinavir has the trade name: Crixivan®.

Nelfinavir Nelfinavir has the trade name Viracept®.

Amprenavir Amprenavir has the trade name Agenerase®. The FDA approved it April 15, 1999, making it the sixteenth FDA-approved antiretroviral. It was the first protease inhibitor approved for twice-a-day dosing instead of needing to be taken every eight hours. The convenient dosing came at a price, as the dose required is 1,200mg, delivered in eight very large gel capsules. Production of Agenerase® was discontinued by the manufacturer December 31, 2004, as it has been superseded by fosamprenavir.

Lopinavir Lopinavir is only marketed as a combination. See Kaletra® below.

Atazanavir Atazanavir has the trade name Reyataz®.

Fosamprenavir Fosamprenavir, with the trade name Lexiva®, is a pro-drug of amprenavir. The FDA approved it October 20, 2003. The human body metabolizes fosamprenavir in order to form amprenavir, which is the active ingredient. That metabolization increases the duration that amprenavir is available, making fosamprenavir a slow-release version of amprenavir and thus reduces the amount of pills required versus standard amprenavir.

Tipranavir Tipranavir, also known as tipranavir disodium, has the trade name Aptivus®.

References

A brief history of the development of protease inhibitors by Hoffman La Roche, Abbott, and Merck: http://inventors.about.com/library/inventors/bl_protease_inhibitors.htm

Neuraminidase inhibitors

Neuraminidase inhibitors are a class of antiviral drugs whose mode of action relies on blocking the function of viral neuraminidase protein, thus preventing the virus from budding from the host cell.

Oseltamivir, Zanamivir and Peramivir belong to this class.

Unlike the M2 inhibitors, which work only against the influenza A, neuraminidase inhibitors act against both influenza A and B.

Reference

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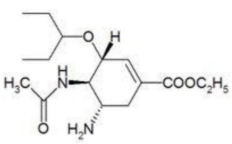
Oseltamivir



Systematic (IUPAC) name

(3R,4R,5S)-4-acetylamino-5-amino-3-(1-ethylpropoxy)-1-cyclohexene-1-carboxylic acid ethyl ester

Identifiers

CAS number 196618-13-0

ATC code J05**AH02**

PubChem 65028

DrugBank APRD01148

Chemical data

Formula C***16***H***28***N***2***O***4***

Mol. weight 312.4 g/mol

Pharmacokinetic data

Bioavailability **75%**

Metabolism hepatic, to GS4071

Half life 6–10 hours

Excretion renal (GS4071)

Therapeutic considerations

Pregnancy cat. B1 (Australia), C (U.S.)

Legal status Schedule 4 (Australia), POM (UK), -only (U.S.)

Routes oral

Oseltamivir (INN) (IPA: [Rs[lÈtæmjvir]) is an antiviral drug that is used in the treatment and prophylaxis of both Influenzavirus A and Influenzavirus B. Like zanamivir, oseltamivir is a neuraminidase inhibitor. It acts as a transition-state analogue inhibitor of influenza neuraminidase, preventing new viruses from emerging from infected cells.

Oseltamivir was the first orally active neuraminidase inhibitor commercially developed. It is a prodrug, which is hydrolysed hepatically to the active metabolite, the free carboxylate of oseltamivir (GS4071). It was developed by Gilead Sciences and is currently marketed by Hoffmann-La Roche (Roche) under the trade name *Tamiflu*. It is generally available by prescription only.

With increasing fears about the potential for a new influenza pandemic, oseltamivir has received substantial media attention. Production capacity is limited, and governments (and even some private individuals) are stockpiling the drug.

Clinical use

Indications and dosage

Oseltamivir is indicated for the treatment of infections due to influenza A and B virus in people at least one year of age, and prevention of influenza in people at least 1 year or older. The usual adult dosage for treatment of influenza is 75 mg twice daily for 5 days, beginning within 2 days of the appearance of symptoms and with decreased doses for children and

patients with renal impairment. Oseltamivir may be given as a preventive measure either during a community outbreak or following close contact with an infected individual. Standard prophylactic dosage is 75 mg once daily for patients aged 13 and older, which has been shown to be safe and effective for up to six weeks. (Roche, 2005; Rossi, 2006)

Use in avian influenza

It has also been found that the standard recommended dose incompletely suppresses viral replication in at least some patients with H5N1 influenza, rendering therapy ineffective and increasing the risk of viral resistance (de Jong et al. 2005). Accordingly, it has been suggested that higher doses and longer durations of therapy should be used for treatment of patients with the H5N1 virus (de Jong et al. 2005, Ward et al. 2005). See Resistance section, below.

Chokephaibulkit et al recommend the use of oseltamivir in pediatric patients, based on experience with one patient.

After following WHO protocols in treating 41 victims of the H5N1 bird flu virus (19% of the world-wide cases of bird flu reported to date), Nguyen Tuong Van, MD, who runs the intensive care unit of the Center for Tropical Diseases in Hanoi, Vietnam concluded that Tamiflu, the drug most widely stockpiled around the world to combat a potential bird flu pandemic, is "useless." According to this article, the WHO confirmed Van's experience stating that Tamiflu has not been "widely successful in human patients", but speculated the drug has not been administered until late in the disease in many Asian countries.

Co-administration with probenecid

It has been suggested that co-administration of oseltamivir with probenecid could extend the limited supply of oseltamivir. Probenecid reduces renal excretion of the active metabolite of oseltamivir. One study showed that 500 mg of probenicid given every six hours doubled both the peak plasma concentration (Cmax) and the half-life of oseltamivir, increasing overall systemic exposure (AUC) by 2.5-fold. (Hill et al., 2002) Although the evidence for this interaction comes from a study by Roche, it was publicised only in October 2005 by a doctor who had reviewed the data (Butler, 2005). Probenecid was used in similar fashion during World War II to extend limited supplies of penicillin, and is still currently used to increase penicillin concentrations in serious infections.

Dosage forms

Oseltamivir is marketed by Roche under the trade name Tamiflu, as capsules (containing oseltamivir phosphate 98.5 mg equivalent to oseltamivir 75 mg) and as a powder for oral suspension (oseltamivir phosphate equivalent to oseltamivir 12 mg/mL).

Adverse effects

Common adverse drug reactions (ADRs) associated with oseltamivir therapy include: nausea, vomiting, diarrhea, abdominal pain, and headache. Rare ADRs include: hepatitis and elevated liver enzymes, rash, allergic reactions including anaphylaxis, and Stevens-Johnson syndrome. (Rossi, 2006)

Various other ADRs have been reported in postmarketing surveillance including: toxic epidermal necrolysis, cardiac arrhythmia, seizure, confusion, aggravation of diabetes, and haemorrhagic colitis.

Neurological effects

In May 2004, the safety division of Japan's health ministry ordered changes to the literature accompanying oseltamivir to add neurological and psychological disorders as possible adverse effects, including: impaired consciousness, abnormal behavior, and hallucinations. Various cases of psychological disorders were associated with oseltamivir therapy between 2000–2004, including several deaths.

On 2005-11-18 the United States Food and Drug Administration (FDA) issued a report regarding the paediatric safety of oseltamivir, which stated that there was insufficient evidence to claim a causal link between oseltamivir use and the deaths of 12 Japanese children (only two from neurological problems). However, it was recommended that a warning was added to the Product Information regarding rashes associated with oseltamivir therapy (Pediatric Advisory Committee, 2005).

In November 2006, reports of bizarre behavior in Japanese children, including three deaths from falls, resulted in the FDA amending the warning label to include possible side effects of delirium, hallucinations, or other related behavior.[1]

Mode of action

Oseltamivir is a neuraminidase inhibitor. By blocking the activity of the neuraminidase, Oseltamivir prevents new viral particles from being released by infected cells.

Resistance

As with other antivirals, resistance to the agent was expected with widespread use of oseltamivir, though the emergence of resistant viruses was expected to be less frequent than with amantadine or rimantadine. The resistance rate reported during clinical trials up to July 2004 was 0.33% in adults, 4.0% in children, and 1.26% overall. Mutations conferring resistance are single amino acid residue substitutions in the neuraminidase enzyme (Ward et al., 2005).

Mutant H3N2 influenza A virus isolates resistant to oseltamivir were found in 18% of a group of 50 Japanese children treated with oseltamivir (Kiso et al., 2004). This rate was similar to another study where resistant isolates of H1N1 influenza virus were found in 16.3% of another cohort of Japanese children (Ward et al., 2005). Several explanations were proposed by the authors of the studies for the higher-than-expected resistance rate detected. First, children typically have a longer infection period, giving a longer time for resistance to

develop. Second, Kiso et al. (2004) claim to have used more rigorous detection techniques than previous studies. Third, the dosage regimen in Japan is different from that of other nations, and some children may have been given a suboptimal dosage of oseltamivir.

High-level resistance has been detected in one girl suffering from H5N1 avian influenza in Vietnam. She was being treated with oseltamivir at time of detection (Le et al., 2005; World Health Organization, 2005).

de Jong et al. (2005) describe resistance development in two more Vietnamese patients suffering from H5N1, and compare their cases with six others. They suggest that the emergence of a resistant strain may be associated with a patient's clinical deterioration. They also note that the recommended dosage of oseltamivir does not always completely suppress viral replication, a situation that could favor the emergence of resistant strains. Moscona (2005) gives a good overview of the resistance issue, and says that personal stockpiles of Tamiflu could lead to under-dosage and thus the emergence of resistant strains of H5N1.

Resistance is of concern in the scenario of an influenza pandemic (Wong and Yuen 2005), and may be more likely to develop in avian influenza than seasonal influenza due to the potentially longer duration of infection by novel viruses. Kiso et al. (2004) suggest that "a higher prevalence of resistant viruses should be expected" during a pandemic.

The genetic sequence for the neuraminidase enzyme is highly conserved across virus strains. This means that there are relatively few variations, and there is also evidence that variations that do occur tend to be less "fit." Thus, mutations that convey resistance to oseltamivir may also tend to cripple the virus by giving it an otherwise less-functional enzyme. The lack of variation in neuraminidase gives two advantages to oseltamivir and zanamivir, the drugs that target that enzyme. First, these drugs work on a broader spectrum of influenza strains. Second, the development of a robust, resistant virus strain appears to be less likely (Ward et al., 2005). It is worth noting that the oseltamivir-resistant strains detected by Kiso et al. (2004) all appeared within individual children after treatment with oseltamivir – the children did not catch the resistant strains in human-to-human or bird-to-human transmission.

Pandemic fears

Oseltamivir was widely used during the H5N1 avian influenza epidemic in Southeast Asia in 2005. In response to the epidemic, various governments – including those of the United Kingdom, Canada, United States and Australia – stockpiled quantities of oseltamivir in preparation for a possible pandemic. Though large, the quantities stockpiled would not have been sufficient to protect the entire population of these countries.

In October 2005, the Indian drug company Cipla announced their plan to begin manufacture of generic oseltamivir without license from Roche. Most patent laws allow governments to authorise supply from generic companies, subject to remuneration to patent owners to address public health problems, including emergencies, although Roche has announced its intention to remain the sole supplier of the drug. Cipla argues that it can legally sell oseltamivir to India and 49 other developing countries, possibly as early as January 2006. Also in October, it was announced that Roche was in discussions with four generic drug manufacturers about the possibility of issuing sublicenses to increase production.

In late October 2005, Roche announced that it was suspending shipments to pharmacies in the United States and Canada until the North American seasonal flu outbreak began, to address concerns about private stockpiling and to preserve supplies for seasonal influenza. It said that, when distribution resumes in Canada, the remaining available drug will be saved for use in high-risk settings like long-term care facilities and hospitals. ales were suspended in Hong Kong as well, and on November 8, also in China. Roche said it would instead send all supplies to China's health ministry.

On November 9, 2005, Vietnam became the first country to be granted permission by Roche to produce a generic version of oseltamivir. The week before, Thai authorities said they would begin producing generic oseltamivir, claiming that Roche had not patented Tamiflu in Thailand. The first Thai generic oseltamivir was produced in February 2006 and are to be available to the public in July 2006.

In December 2005, Roche also signed a sublicense for complete oseltamivir production with China's Shanghai Pharmaceuticals, and by March 2006 a sublicense had also been granted to India's Hetero. In June 2006, the Chinese government gave Shanghai Pharmaceuticals permission to proceed, based upon tests of the domestic production. The company said it planned to market the drug by the end of the month.

In late May 2006, the World Health Organization asked Roche to be ready to ship an emergency stockpile of oseltamivir to Indonesia if needed. The alert was in response to suspected human-to-human transmission within a family and was planned to last for two weeks

U.S. Government policy and oseltamivir

In November, 2005, U.S. president George W. Bush requested that Congress fund $7.1 billion in emergency spending for flu pandemic preparedness (the Senate had already passed an $8.1 billion bill). Bush's plan included $1.4 billion for government purchases of antiviral drugs.

Some commentators question the motives of the U.S. government's endorsement and planned purchase of oseltamivir, noting Secretary of Defense Donald Rumsfeld's close ties to Gilead Sciences, rightsholder to the oseltamivir patent. Rumsfeld is a former chairman of Gilead, and federal disclosure forms indicate that he owns between USD$5 million and USD$25 million in Gilead stock (Schwartz 2005). The rise in Gilead's share prices from USD$35 to USD$57 per share will have added between USD$2.5 million to USD$15.5 million to Rumsfeld's net worth.

On the other hand, at least one Democratic Senator has criticized Bush for not planning to buy enough antiviral drugs

Personal stockpiling of oseltamivir

The short supply of oseltamivir has prompted some individuals to stockpile the drug. Several American states, including Massachusetts and Colorado, have issued advisories strongly discouraging this practice.

One argument against individual stockpiling is that limited drugs should be kept for more strategic or ethical deployment, that is, to hard-hit areas, to people in critical roles (e.g., healthcare and government workers), to people vulnerable to seasonal flu, or to people who actually have come down with avian influenza. Ethical arguments are sometimes made: Why should affluent people (or nations) have preferred access to antiviral medications? Illegal importation may divert the drug from poorer countries where the risk of avian influenza is actually higher.

In the New England Journal of Medicine, Moscona (2005) argues that the use of personal stockpiles of oseltamivir could result in the administration of low dosages, allowing for the development of drug-resistant virus strains. Many stockpilers will only have ten 75 mg pills (the current recommended dosage for oseltamivir), but this may be insufficient for the treatment of H5N1. (de Jong et al., 2005)

Another argument is that it would be difficult for home users to determine whether illegally-imported Tamiflu is counterfeit. This is genuinely a potential problem, but, in the face of a shortage, some individuals may be willing to face such a risk. In December 2005, 53 packages of counterfeit Tamiflu tablets were intercepted by the US Customs Service in South San Francisco. The packages were labeled "Generic Tamiflu". Roche officials know of only one instance of counterfeit Tamiflu appearing outside of the United States: incorrectly-labelled tablets found in Holland, which contained only Vitamin C and lactose. However, sophisticated criminals could produce convincing fake packaging in the future

A fourth purported problem is that the H5N1 virus can be reliably diagnosed only in a small number of labs around the world; therefore, there is no way for home users to know whether flu-like symptoms are the result of avian flu or a more benign ailment. This argument lacks face validity, since treatment must begin before such tests results would be available anyway.

Veterinary use

Oseltamivir appears to be active against canine parvovirus, feline panleukopenia, the canine respiratory complex known as "kennel cough," and the emerging disease dubbed "canine flu", an equine virus that began affecting dogs in 2005. Veterinary investigation of its use for canine parvo and canine flu is ongoing, but many shelters and rescue groups have reported great success employing oseltamivir in the early stages of these illnesses.

Chemical synthesis

Commercial syntheses

The current production method includes two reaction steps with potentially hazardous azides.

The synthesis commences from naturally available ()-shikimic acid. The 3,4-pentylidene acetal mesylate is prepared in three steps: esterification with ethanol and thionyl chloride; ketalization with para-toluenesulfonic acid and 3-pentanone; and mesylation with triethylamine and methanesulfonyl chloride. Reductive opening of the ketal under modified

Hunter conditions (JOC 1993, 58, 6756) in dichloromethane yields an inseparable mixture of isomeric mesylates. The corresponding epoxide is formed under basic conditions with potassium bicarbonate. Using the inexpensive Lewis acid magnesium bromide diethyl etherate (commonly prepared fresh by the addition of magnesium turnings to 1,2-dibromoethane in benzene:diethyl ether), the epoxide is opened with allyl amine to yield the corresponding 1,2-amino alcohol. The water-immiscible solvents methyl tert-butyl ether and acetonitrile are used to simplify the workup procedure, which involved stirring with 1 M aqueous ammonium sulfate. Reduction on palladium, promoted by ethanolamine, followed by acidic workup yielded the deprotected 1,2-aminoalcohol. The aminoalcohol was converted directly to the corresponding allyl-diamine in an interesting cascade sequence that commences with the unselective imination of benzaldehyde with azeotropic water removal in methyl tert-butyl ether. Mesylation, followed by removal of the solid byproduct triethylamine hydrochloride, results in an intermediate that was poised to undergo aziridination upon transimination with another equivalent of allylamine. With the librated methanesulfonic acid, the aziridine opens cleanly to yield a diamine that immediately undergoes a second transimination. Acidic hydrolysis then removed the imine. Selective acylation with acetic anhydride (under buffered conditions, the 5-amino group is protonated owing to a considerable difference in pKa, 4.2 vs 7.9, preventing acetylation) yields the desired N-acetylated product in crystalline form upon extractive workup. Finally, deallylation as above, yielded the freebase of oseltamivir, which was converted to the desired oseltamivir phosphate by treatment with phosphoric acid. The final product is obtained in high purity (99.7%) and an overall yield of 17-22% from ()-shikimic acid. It is noted that the synthesis avoids the use of potentially explosive azide reagents and intermediates; however, the synthesis actually used by Roche uses azides. Roche has other routes to oseltamivir that do not involve the use of ()-shikimic acid as a chiral pool starting material, such as a Diels-Alder route involving furan and ethyl acrylate or an isophthalic acid route, which involves catalytic hydrogenation and enzymatic desymmetrization.

2006 Corey synthesis

In 2006 the group of E.J. Corey published a novel route also bypassing shikimic acid starting from butadiene and acrylic acid. The inventors choose not to patent this procedure which is described below. Strictly speaking the synthesis is a formal total synthesis, as the final product to be characterized was the BOC-derivative.

Butadiene 1 reacts in an asymmetric Diels-Alder reaction with the esterfication product of acrylic acid and 2,2,2-Trifluoroethanol 2 catalysed by the CBS catalyst. The ester 3 is converted into an amide in 4 by reaction with ammonia and the next step to lactam 5 is an iodolactamization with iodine initiated by trimethylsilyltriflate. The amide group is fitted with a BOC protective group by reaction with Boc anhydride in 6 and the iodine substituent is removed in an elimination reaction with DBU to the alkene 7. Bromine is introduced in 8 by an allylic bromination with NBS and the amide group is cleaved with ethanol and caesium carbonate accompanied by elimination of bromide to the diene ethyl ester 9. The newly formed double bond is functionalized with N-bromoacetamide 10 catalyzed with Tin(IV) bromide with complete control of stereochemistry. In the next step the bromine atom in 11

is displaced by the nitrogen atom in the amide group with the strong base KHMDS to the aziridine 12 which in turn is opened by reaction with 3-pentanol 13 to the ether 14. In the final step the BOC group is removed with phosphoric acid and the oseltamivir phosphate *15* is formed.

Production shortage/shikimic acid

In early 2005, Roche announced a production shortage. (See Pandemic Fears, below). According to Roche, the major bottleneck in oseltamivir production is the availability of shikimic acid, which cannot be synthesised economically and is only effectively isolated from Chinese star anise, an ancient cooking spice. Although most autotrophic organisms produce shikimic acid, the isolation yield is low. A shortage of star anise is one of the key reasons why there is a worldwide shortage of Tamiflu (as at 2005). Star anise is grown in four provinces in China and harvested between March and May. It is also produced in Lang Son province, Vietnam. The shikimic acid is extracted from the seeds in a ten-stage manufacturing process. Thirteen grams of star anise make 1.3 grams of shikimic acid, which can be made into 10 oseltamivir 75 mg capsules. Ninety percent of the harvest is already used by Roche in making oseltamivir.

Some academic experts and other drug companies are disputing the difficulty of producing shikimic acid by means other than star anise extraction. An alternative method for production of the acid involves fermentation of genetically-modified bacteria. Other potential sources of shikimic acid include the ginkgo tree. In addition, quinic acid, derived from the bark of the cinchona tree of the Democratic Republic of the Congo, is a potential alternative base material for the production of oseltamivir.

However, as is clear by the multistep synthesis shown above, although the major bottleneck for Roche may be the availability of shikimic acid, production of oseltamivir is very involved. Increasing production volume (by Roche or others) would require construction of extensive new facilities (which may not be amenable to scaleup and, even if identical on paper, may not necessarily produce acceptable yields), and even if current facilities could handle a larger feedstock quantity, there would be a delay in production as the material makes it down the pipeline (~6 months or so).

In March 2006, Roche announced that it was making utilizing the resources of 15 external contractors in 9 countries, allowing production to expand to "as much as 400 million doses annually by the end of this year"

Canadian generic drug company Apotex is attempting to modify Oseletamivir to use a synthetic alternative to shikimic acid.

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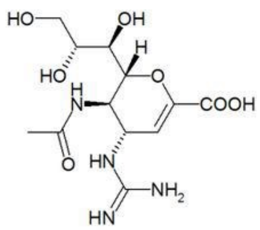
See also

- Zanamivir **- another** neuraminidase inhibitor

Zanamivir



Systematic (IUPAC) name

5-acetamido-4-guanidino-6-(1,2,3-trihydroxypropyl)-
5,6-dihydro-4H-pyran-2-carboxylic acid

Identifiers

CAS number 139110-80-8

ATC code J05**AH01**

PubChem 60855

DrugBank APRD00378

Chemical data

Formula $C_{12}H_{20}N_4O_7$

Mol. weight 332.31 g/mol

Pharmacokinetic data

Bioavailability **2% (oral)**

Protein binding <10%

Metabolism Negligible

Half life 2.5–5.1 hours

Excretion Renal

Therapeutic considerations

Pregnancy cat. B1 (Au)

Legal status S4 $_{\text{(Au)}}$, POM $_{\text{(UK)}}$, -only $_{\text{(U.S.)}}$

Routes Inhalation

Zanamivir (INN) (IPA: [zYÈnæmjvir]) is a neuraminidase inhibitor used in the treatment of and prophylaxis of both Influenzavirus A and Influenzavirus B. Zanamivir was the first neuraminidase inhibitor commercially developed. It is currently marketed by GlaxoSmithKline under the trade name *Relenza*.

Development

Zanamivir was developed in 1989 by scientists at the Australian biotechnology company Biota, working in conjunction with the CSIRO and the Victorian College of Pharmacy. The development was part of Biota's ongoing program to develop antiviral agents through rational drug design.

The strategy relied on the availability of the crystal structure of influenza neuraminidase which was achieved by x-ray crystallography. It was known as far back as 1974 that 2-deoxy-2,3-didehydro-N-acetylneuraminic acid (DANA), a sialic acid analogue, was an inhibitor of neuraminidase.[1] Using the crystal structure of neuraminidase and DANA as a starting point, the researchers employed a computer-aided process to attempt to design a molecule which was a better fit for (and therefore inhibited) the active site of neuraminidase. Zanamivir, a transition-state analogue inhibitor of neuraminidase, was the result.[2]

In 1990, zanamivir was licensed to Glaxo (now GlaxoSmithKline) for exclusive worldwide development and marketing. In 1999, the product was approved for marketing in the US and subsequently has been registered by GSK in a total of 70 countries.

Limitations

Whilst zanamivir proved to be a potent and effective inhibitor of influenza neuraminidase and inhibitor of influenza virus replication in vitro and in vivo, this didn't necessarily translate into a successful clinical treatment for influenza. In clinical trials it was found that zanamivir was able to reduce the time to symptom resolution by 1.5 days provided therapy was started within 48 hours of the onset of symptoms.

A further limitation concerns the poor oral bioavailability of zanamivir. This meant that oral dosing was impossible, limiting dosing to the parenteral routes. Zanamivir, therefore, is administered by inhalation - a route that was chosen for patient compliance with therapy. But even this route of administration is not acceptable to many in the community.

Commercial difficulties

Biota, being only a small company, was not able to bring the drug to market by itself. Consequently, it was licensed to Glaxo (now GlaxoSmithKline) to complete development and to market internationally as Relenza, delivered via Glaxo's proprietary, and some would say cumbersome, Diskhaler inhalation device. The license agreement entitled Biota to receive a 7% royalty on Glaxo's sales of Relenza.

A combination of factors has resulted in the limited commercial success of zanamivir (Relenza). The relatively small effect on the timecourse of influenza symptoms, the inhalation dosage form, a less-than-ideal device, and high expense make it a difficult product to market well. And although zanamivir was the first neuraminidase inhibitor to the market, it had only a few months lead over the second entrant, oseltamivir (Tamiflu), with an oral formulation much preferred by patients. Faced with this competition, GSK effectively abandoned the product.

When first marketed in 1999/00, Relenza captured close to 50% of the global market for neuraminidase inhibitors. But after the launch year, GSK cut virtually all promotion and other support for Relenza, allowing the product's sales and market share to slide in every major market over the following four years. By 2004 Relenza held only a 3% share of the estimated US$330 million global market.

In May 2004, Biota issued a writ against GSK for failing to support and promote Relenza. The writ claimed that GSK was in breach of several obligations:

- GSK restricted Relenza to its proprietary Diskhaler system, and did not adequately pursue alternative or improved inhalation systems.
- GSK withdrew support for crucial post-approval clinical studies designed to expand the product's use and market acceptance.
- After the launch year, GSK failed to properly launch Relenza in a number of countries where the product was registered, and allowed registrations to be stopped, cancelled or scheduled for cancellation.
- After the launch year, GSK withdrew promotion support for Relenza, allowing the sales and market share to decline in all key markets, even in those markets where there was no direct competition.

Developments from zanamivir

Zanamivir was the first of the neuraminidase inhibitors. Despite the limited commercial success of this drug, the work and strategies employed in the development of zanamivir were important first-steps in the development of further members of this class including oseltamivir and the candidate drug RWJ-270201 (Phase I trials). As a result more effective and potent treatments for influenza may be developed in the future.

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Interferon

Interferon alpha 1 *Identifiers*

Symbol(s) IFNA1

Entrez 3439

OMIM **147660**

RefSeq NM_024013

UniProt P01562

Other data

Locus Chr. 9 p22

Interferon alpha 2 *Identifiers*

Symbol(s) IFNA2

Entrez 3440

OMIM **147562**

RefSeq NM_000605

UniProt P01563

Other data

Locus Chr. 9 p22

Interferon alpha 4 *Identifiers*

Symbol(s) IFNA4

Entrez 3441

OMIM **147564**

RefSeq NM_021068

UniProt P05014

Other data

Locus Chr. 9 p22

Interferon alpha 5 *Identifiers*

Symbol(s) IFNA5

Entrez 3442

OMIM **147565**

RefSeq NM_002169

UniProt P01569

Other data

Locus Chr. 9 p22

Interferon alpha 6 *Identifiers*

Symbol(s) IFNA6

Entrez 3443

OMIM **147566**

RefSeq NM_021002

UniProt P05013

Other data

Locus Chr. 9 p22

Interferon alpha 7 *Identifiers*

Symbol(s) IFNA7 IFNA-J

Entrez 3444

OMIM **147567**

RefSeq NM_021057

UniProt P01567

Other data

Locus Chr. 9 p22

Interferon alpha 8 *Identifiers*

Symbol(s) IFNA8

Entrez 3445

OMIM **147568**

RefSeq NM_002170

UniProt P32881

Other data

Locus Chr. 9 p22

Interferon alpha 10 *Identifiers*

Symbol(s) IFNA10

Entrez 3446

OMIM **147577**

RefSeq NM_002171

UniProt P01566

Other data

Locus Chr. 9 p22

Interferon alpha 13 *Identifiers*

Symbol(s) IFNA13

Entrez 3447

OMIM **147578**

RefSeq NM_006900

UniProt P01562

Other data

Locus Chr. 9 p22

Interferon alpha 14 *Identifiers*

Symbol(s) IFNA14

Entrez 3448

OMIM **147579**

RefSeq NM_002172

UniProt P01570

Other data

Locus Chr. 9 p22

Interferon alpha 16 *Identifiers*

Symbol(s) IFNA16

Entrez 3449

OMIM **147580**

RefSeq NM_002173

UniProt P05015

Other data

Locus Chr. 9 p22

Interferon alpha 17 *Identifiers*

Symbol(s) IFNA17

Entrez 3451

OMIM **147583**

RefSeq NM_021268

UniProt P01571

Other data

Locus Chr. 9 p22

Interferon alpha 21 *Identifiers*

Symbol(s) IFNA21

Entrez 3452

OMIM **147584**

RefSeq NM_002175

UniProt P01568

Other data

Locus Chr. 9 p22

Interferon beta 1 *Identifiers*

Symbol(s) IFNB1 IFNB

Entrez 3456

OMIM **147640**

RefSeq NM_002176

UniProt P01574

Other data

Locus Chr. 9 p22

Interferon beta 3 *Identifiers*

Symbol(s) IFNB3

Entrez 3457

OMIM **147860**

RefSeq [1]

UniProt [2]

Other data

Locus Chr. 8 [3]

Interferon delta *Identifiers*

Symbol(s) IFND1

Entrez [4]

RefSeq [5]

UniProt P37290

Other data

Locus Chr. [6] Interferon kappa *Identifiers*

Symbol(s) IFNK

Entrez 56832

RefSeq **NM_020124**

UniProt Q9P0W0

Other data

Locus Chr. 9 p21.2 Interferon omega 1 *Identifiers*

Symbol(s) IFNW1

Entrez 3467

OMIM **147553**

RefSeq NM_002177

UniProt P05000

Other data

Locus Chr. 9 p22

Interferons (IFNs) are natural proteins produced by the cells of the immune system of most vertebrates in response to challenges by foreign agents such as viruses, bacteria, parasites and tumor cells. Interferons belong to the large class of glycoproteins known as cytokines.

The discovery of interferon

While aiming to develop an improved vaccine for smallpox, two Japanese virologists, Yasu-ichi Nagano and Yasuhiko Kojima working at the then Institute for Infection Disease at the University of Tokyo, noticed that rabbit-skin or testis previously inoculated with UV-inactivated virus exhibited inhibited viral growth when re-infected at the same site with live virus. They hypothesised that this was due to some “facteur inhibiteur” (inhibitory factor), and began to characterise it by fractionation of the UV-irradiated viral homogenates using an ultracentrifuge. They published these findings in 1954 in the French journal now known as “Journal de la Société de Biologie”.[1] While this paper demonstrated that the activity could be separated from the virus particles, it could not reconcile the antiviral activity demonstrated in the rabbit skin experiments, with the observation that the same supernatant led to the production of antiviral antibodies in mice. A further paper in 1958, involving triple-ultracentrifugation of the homogenate demonstrated that the inhibitory factor was distinct from the virus particles, leading to trace contamination being ascribed to the 1954 observations.[2][3]

Meanwhile, the Scottish virologist Alick Isaacs and the Swiss researcher Jean Lindenmann, at the National Institute for Medical Research in London, noticed an interference effect caused by heat-inactivated influenza virus on the growth of live influenza virus in fragments of chick chorioallantoic membrane. They published their results in 1957;[4] in this paper they coined the term ‘interferon’, and today that specific interfering agent is known as a ‘Type I interferon’.

Nagano’s work was never fully appreciated in the scientific community; possibly because it was printed in French, but also because his in vivo system was perhaps too complex to provide clear results in the characterisation and purification of interferon. As time passed, Nagano became aware that his work had not been widely recognised, yet did not actively seek reevaluation of his status in field of interferon research. As such, the majority of the credit for discovery of the interferon goes to Isaacs and Lindenmann, with whom there is no record of Nagano ever having made personal contact.[5]

Types of interferon

Three major classes of interferons have been described for humans, Type I, type II and type III, classified based on the type of receptor through which they signal.

Type I IFN

Human type I IFNs comprise a vast and growing group of IFN proteins, designated IFN-± (alpha), IFN-² (beta), IFN-º (kappa), IFN-´ (delta), IFN-µ (epsilon), IFN-Ä (tau), IFN-É (omega) and IFN-¶ (zeta, also known as limitin)[6].[7] The IFN-± proteins come in 13 subtypes that are called IFNA1, IFNA2, IFNA4, IFNA5, IFNA6, IFNA7, IFNA8, IFNA10, IFNA13, IFNA14, IFNA16, IFNA17, IFNA21. These genes for these IFN-± molecules are found together in a cluster on chromosome 9. Two types of IFN-² have been described, IFN-²1 and IFN-²3[8] (a gene designated IFN-²2 is actually IL-6). IFN-µ, –º, -Ä, and –¶ appear, at this time, to come in

a single isoform in humans. IFN-É, although having only one functional form described to date, has several pseudogenes.[9][10][11][12][13][14][15] Homologous molecules to type I IFNs are found in many species, including most mammals, and some have been identified in birds, reptiles, amphibians and fish species.[16] All type I IFNs bind to a specific cell surface receptor complex known as the IFN-± receptor (IFNAR) that consists of IFNAR1 and IFNAR2 chains.

Type II IFN

A sole member makes up the type II IFNs that is called IFN-³ (gamma). Mature IFN-³ is an anti-parallel homodimer, which binds to the IFN-³ receptor (IFNGR) complex to elicit a signal within its target cell. IFNGR is made up of two subunits each of molecules designated IFNGR1 and IFNGR2.

Type III IFN

The recently classified type III IFN group consists of three IFN-» (lamda) molecules called IFN-»1, IFN-»2 and IFN-»3 (also called IL29, IL28A and IL28B respectively).[17] These IFNs signal through a receptor complex consisting of IL10R2 (also called CRF2-4) and IFNLR1 (also called CRF2-12). [18]

The signaling pathway of interferons

While there is evidence to suggest other signaling mechanisms exist, the JAK-STAT signaling pathway is the best-characterised and commonly accepted IFN signaling pathway.

Sources and functions of inteferons

Interferons in general have several effects in common. They are antiviral and possess antioncogenic properties, macrophage and natural killer lymphocyte activation, and enhancement of major histocompatibility complex glycoprotein classes I and II, and thus presentation of foreign (microbial) peptides to T cells. In a majority of cases, the production of interferons is induced in response to microbes such as viruses and bacteria and their products (viral glycoproteins, viral RNA, bacterial endotoxin, bacterial flagella, CpG DNA), as well as mitogens and other cytokines, for example interleukin 1, interleukin 2, interleukin-12, tumor necrosis factor and colony-stimulating factor, that are synthesised in the response to the appearance of various antigens in the body. Their metabolism and excretion take place mainly in the liver and kidneys. They rarely pass the placenta and the blood-brain barrier.

Type I interferons

IFN-± and IFN-² are secreted by many cell types including lymphocytes (NK cells, B-cells and T-cells), macrophages, fibroblasts, endothelial cells, osteoblasts and others. They

stimulate both macrophages and NK cells to elicit and anti-viral response, and are also active against tumors. IFN-É is released by leukocytes at the site of viral infection or tumors.

Type II interferons

IFN-^{3} is involved in the regulation of the immune and inflammatory responses; in humans, there is only one type of interferon-gamma. It is produced in activated T-cells and natural killer cells. IFN-^{3} has some anti-viral and anti-tumor effects, but these are generally weak. However, this cytokine potentiates the effects of the type I IFNs. IFN-^{3} released by Th1 cells recruits leukocytes to a site of infection, resulting in increased inflammation. It also stimulates macrophages to kill bacteria that have been engulfed. IFN-^{3} released by Th1 cells is also important in regulating the Th2 response. As IFN-^{3} is vitally implicated in the regulation of immune response, its production can lead to autoimmune disorders.

Viral induction of interferons

All classes of interferon are very important in fighting RNA virus infections. However, their presence also accounts for some of the host symptoms, such as sore muscles and fever. They are secreted when abnormally large amounts of dsRNA are found in a cell. dsRNA is normally present in very low quantities. The dsRNA acts like a trigger for the production of interferon. The gene that codes for this cytokine is switched on in an infected cell, and the interferon synthesized and secreted to surrounding cells.

As the original cell dies from the cytolytic RNA virus, these thousands of viruses will infect nearby cells. However, these cells have received interferon, which essentially warns these other cells that there's a wolf in the pack of sheep. They then start producing large amounts of a protein known as protein kinase R (or PKR). If a virus chooses to infect a cell that has been “pre-warned” by interferon, it is like charging into a hail of bullets for the virus. The PKR is activated by the dsRNA, and begins transferring phosphate groups (phosphorylating) to a protein known as eIF2, a eukaryotic translation initiation factor. After phosphorylation, eIF2 has a reduced ability to initiate translation, the production of proteins coded by cellular mRNA. This prevents viral replication, but also inhibits normal cell ribosome function, killing both the virus and the host cell if the response is active for a sufficient amount of time. All RNA within the cell is also degraded, preventing the mRNA from being translated by eIF2 if some of the eIF2 failed to be phosphorylated.

Pharmaceutical uses

Interferon was scarce and expensive until 1980 when the interferon gene was inserted into bacteria using recombinant DNA technology, allowing mass cultivation and purification from bacterial cultures. Several different types of interferon are now approved for use in humans, and interferon therapy is used (in combination with chemotherapy and radiation) as a treatment for many cancers. When used in the systemic therapy, IFN-± and IFN-^{3} are mostly administered by an intramuscular injection. The injection of interferons in the muscle, in the vein, or under skin is generally well tolerated. The most frequent side-effects

are flu-like symptoms: increased body temperature, feeling ill, fatigue, headache, muscle pain, convulsion, dizziness, hair thinning, and depression. Erythema, pain and hardness on the spot of injection are also frequently observed. All known effects are usually reversible and disappear a few days after the therapy has been finished. However, there are some serious side effects and the patient is advised to read the accompanying pamphlet.

More than half of hepatitis C patients treated with interferon respond with better blood tests and better liver biopsies. There is some evidence that giving interferon immediately following infection can prevent hepatitis C; however, people infected by hepatitis C often do not display symptoms of HCV until months or years later.

More recently, the FDA approved pegylated interferon-alpha, in which polyethylene glycol is added to make the interferon last longer in the body. (Pegylated interferon-alpha-2b was approved in January 2001; pegylated interferon-alpha-2a was approved in October 2002.) The pegylated form is injected once weekly, rather than three times per week for conventional interferon-alpha. Used in combination with the antiviral drug ribavirin, pegylated interferon produces sustained cure rates of 75% or better in people with genotype 2 or 3 hepatitis C (which is easier to treat) but still less than 50% in people with genotype 1 (which is most common in the U.S. and Western Europe).

Interferon-beta (Interferon beta-1a and Interferon beta-1b) is used in the treatment and control of the neurological disorder multiple sclerosis. By an as-yet-unknown mechanism, interferon-beta inhibits the production of Th1 cytokines and the activation of monocytes.

Administered intranasally in very low doses, interferon is extensively used in Eastern Europe and Russia as a method to prevent and treat viral respiratory diseases such as cold and flu. It is claimed that the treatment can lower the risk of infection by as much as 60-70%. Mechanisms of such action of interferon are not well understood; it is thought that doses must be larger by several orders of magnitude to have any effect on the virus. Consequently, most Western scientists are sceptical of these claims.[19]

Also See

- Immunosuppressive drug

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Disinfectants

Disinfectants are antimicrobial agents that are applied to non-living objects to destroy microorganisms, the process of which is known as *disinfection*. Disinfectants should generally be distinguished from antibiotics that destroy microorganisms within the body, and from antiseptics, which destroy microorganisms on living tissue. Sanitisers are high level

disinfectants that kill over 99.9% of a target microorganism in applicable situations. Not all disinfectants and sanitisers can sterilise (the complete elimination of all microorganisms), and those that can depend entirely on their mode of application. Bacterial endospores are most resistant to disinfectants, however some viruses and bacteria also posess some tolerance.

Properties

The ideal disinfectant would offer complete sterilisation, without harming other forms of life, be inexpensive, and non-corrosive. Unfortunately ideal disinfectants do not exist. All disinfectants are also, by their very nature, potentially harmful (even toxic) to humans or animals. They should be treated with appropriate care. Most come with safety instructions printed on the packaging, which should be read in full before using the disinfectant. Most modern household disinfectants contain Bitrex, an exceptionally bitter substance designed to discourage ingestion, as an added safety measure. Those that are used indoors should never be mixed with other cleaning products as chemical reactions can occur. They are frequently used in hospitals, dental surgeries, kitchens and bathrooms to kill infectious organisms.

The choice of the disinfectant to be used depends on the particular situation. Some disinfectants have a wide spectrum (kill nearly all microorganisms), whilst others kill a smaller range of disease-causing organisms but are preferred for other properties (they may be non-corrosive, non-toxic, or inexpensive).

The disinfecting properties of sunlight (ultra-violet) are powerful. Basic hygiene, rather than total reliance on chemicals, is important in the fight against bacteria, which generally prefer a warm-moist-dark environment. There are arguments for creating or maintaining conditions which are not conducive to bacterial survival and multiplication, rather than attempting to kill them with chemicals. Bacteria have a very rapid multiplication rate, which enables them to 'evolve' rapidly. Should some bacteria survive a chemical attack, they give rise to the next generation. Thus they are able to develop resistance to hostile chemicals. For this reason, some question the wisdom of impregnating cloths, cutting boards and worktops in the home with bactericidal chemicals. Hygiene in is important in prevention of foodborne illness.

Types of disinfectants

Alcohols

Alcohols, usually ethanol or isopropanol, are wiped over benches and skin and allowed to evaporate for quick disinfection. They have wide microbiocidal activity, are non corrosive, but can be a fire hazard. They also have limited residual activity due to evaporation, and have a limited activity in the presence of organic material. Alcohols are more effective combined with water, 70% alcohol is more active than 95% alcohol. Alcohol is not effective against fungal or bacterial spores.

Aldehydes

Aldehydes, such as Glutaraldehyde, have a wide microbiocidal activity and are sporocidal and fungicidal. They are partly inactivated by organic matter and have slight residual activity.

Halogens

- *Chloramine* is used in drinking water treatment instead of chlorine because it produces less disinfection byproducts.
- *Chlorine* is Used to disinfect swimming pools, and is added in small quantities to drinking water to reduce waterborne diseases.
- *Hypochlorites* (Sodium hypochlorite), often in the form of common household bleach, are used in the home to disinfect drains, and toilets. Other hypochlorites such as calcium hypochlorite are also used, especially as a swimming pool additive. Hypochlorite gives off free chlorine and it is the chlorine that is the true disinfectant. Hypobromite solutions are also sometimes used.
- Iodine is usually dissolved in an organic solvent or as Lugol's iodine solution. It is used in the poultry industry. It is added to the birds' drinking water. Although no longer recommended because it increases scar tissue formation and increases healing time, tincture of iodine has also been used as an antiseptic for skin cuts and scrapes.

Oxidising agents

Oxidising agents act by oxidising the cell membrane of microorganisms, which results in a loss of structure and leads to cell lysis and death.

- Chlorine dioxide is used as an advanced disinfectant for drinking water to reduce waterborne diseases. In certain parts of the world, it has largely replaced chlorine because it forms fewer byproducts. Sodium chlorite, sodium chlorate, and potassium chlorate are used as precursors for generating chlorine dioxide.
- Hydrogen peroxide is used in hospitals to disinfect surfaces. It is sometimes mixed with colloidal silver. It is often preferred because it causes far fewer allergic reactions than alternative disinfectants. Also used in the food packaging industry to disinfect foil containers. A 3% solution is also used as an antiseptic. When hydrogen peroxide comes into contact with the catalase enzyme in cells it is broken down into water and a hydroxyl free radical. It is the damage caused by the oxygen free radical that kills bacteria. However, as recent studies have show hydrogen peroxide to be toxic to growing cells as well as bacteria, its use as an antiseptic is no longer recommended.
- Ozone is a gas that can be added to water for sanitation.
- *Peracetic acid* is a disinfectant produced by reacting hydrogen peroxide with acetic acid. It is broadly effective against microorganisms and is not deactivated by catalase and peroxidase, the enzymes which break down

hydrogen peroxide. It also breaks down to food safe and environmentally friendly residues (acetic acid and hydrogen peroxide), and therefore can be used in non-rinse applications. It can be used over a wide temperature range (0-40°C), wide pH range (3.0-7.5), in clean-in-place (CIP) processes, in hard water conditions, and is not affected by protein residues.

- Potassium permanganate ($KMnO_4$) is a red crystalline powder that colours everything it touches, and is used to disinfect aquariums. It is also used widely in community swimming pools to disinfect ones feet before entering the pool. Typically, a large shallow basin of $KMnO_4$/water solution is kept near the pool ladder. Participants are required to step in the basin and then go into the pool. Additionally, it is widely used to disinfect community water ponds and wells in tropical countries, as well as to disinfect the mouth before pulling out teeth. It can be applied to wounds in dilute solution; potassium permanganate is a very useful disinfectant.

Phenolics

Phenolics are the active ingredient in most bottles of "household disinfectant". They are also found in some mouthwashes and in disinfectant soap and handwashes. Phenol is probably the oldest known disinfectant as it was first used by Lister, when it was called carbolic acid. It is rather corrosive to the skin and sometimes toxic to sensitive people, so the somewhat less corrosive phenolic o-phenylphenol is often used in favour. Hexachlorophene is a phenolic which was once used as a germicidal additive to some household products but was banned due to suspected harmful effects.

Quaternary ammonium compounds

Quaternary ammonium compounds (Quats), such as benzalkonium chloride, are a large group of related compounds. Some have been used as a low level disinfectant. They are effective against bacteria, but not against some species of Pseudomonas bacteria or bacterial spores. Quats are biocides which also kill algae and are used as an additive in large-scale industrial water systems to minimize undesired biological growth. Quaternary ammonium compounds can be effective disinfectants against enveloped viruses.

Other

- *Dettol* is used to disinfect surfaces at home. It kills the majority of bacteria. It is one of the few disinfectants useful against viruses.
- *Virkon* is a wide-spectrum disinfectant used in labs. It kills bacteria, viruses, and fungi. It is used as a 1% solution in water, and keeps for one week once it is made up. It is expensive, but very effective, its pink colour fades as it is used up so it is possible to see at a glance if it is still fresh.
- *High-intensity ultraviolet light* can be used for disinfecting smooth surfaces such as dental tools, but not porous materials that are opaque to the light

such as wood or foam. Ultraviolet light fixtures are often present in microbiology labs, and are activated only when there are no occupants in a room (e.g., at night.

Relative effectiveness of disinfectants

One way to compare disinfectants is to compare how well they do against a known disinfectant and rate them accordingly. Phenol is the standard, and the corresponding rating system is called the "Phenol coefficient". The disinfectant to be tested is compared with phenol on a standard microbe (usually Salmonella typhi or Staphylococcus aureus). Disinfectants that are more effective than phenol have a coefficient > 1. Those that are less effective have a coefficient < 1.

Home Disinfectants

By far the most cost-effective home disinfectant is common chlorine bleach (a 5% solution of Sodium hypochlorite which is effective against most common pathogens, including such difficult organisms as HIV, tuberculosis (mycobacterium tuberculosis), hepatitis B and C,funguses, and antibiotic-resistant strains of staphylococcus and enterococcus. It even has some disinfectant action against parasitic organisms [1]. Positives are that it kills the widest range of pathogens of any inexpensive disinfectant; it is extremely powerful against viruses and bacteria at room temperature; it is commonly available and inexpensive; and it breaks down quickly into harmless components (primarily table salt and oxygen). Negatives are that it is caustic to the skin and eyes, especially at higher concentrations; like many common disinfectants, it degrades in the presence of organic substances; it smells bad; it is not effective against giardia lamblia and cryptosporidium; and extreme caution must be taken not to combine it with ammonia or any acid (such as vinegar). The best practice is not to add anything to household bleach except water. Dilute bleach can be tolerated on the skin for a period of time by most persons, as witnessed by the long exposure to extremely dilute "chlorine" (actually sodium or calcium hypochlorite) many children get in swimming pools.

To use chlorine bleach effectively, the surface or item to be disinfected must be clean. In the bathroom, special caution must be taken to wipe up urine. A 1 to 20 solution in water is effective simply by being wiped on and left to dry. The user should wear rubber gloves and, in tight airless spaces, goggles. If parasitic organisms are suspected, it should be applied at 1 to 1 concentration, or even undiluted; extreme caution must be taken to avoid contact with eyes and mucous membranes. Protective goggles and good ventilation are mandatory when applying concentrated bleach.

Where one does not want to risk the corrosive effects of bleach, alcohol-based disinfectants are reasonably inexpensive and quite safe. The great drawback to them is their rapid evaporation; sometimes effective disinfection can be obtained only by immersing an object in the alcohol.

References

1. ^ EPA's Registered Sterilizers, Tuberculocides, and Antimicrobial Products Against HIV-1, and Hepatitis B and Hepatitis C Viruses. *(Obtained January 4, 2006)*

See also

- Antimicrobials
- Antiseptics

Bleach

To *bleach* something is to remove or lighten its color; a "bleach" is a chemical that can produce these effects, often via oxidation. Common chemical bleaches include a solution of sodium hypochlorite (NaOCl), or "chlorine bleach," and "oxygen bleach," which contains hydrogen peroxide or a peroxide-releasing compound such as sodium perborate or sodium percarbonate. "Bleaching powder" is calcium hypochlorite. Bleaching may be a preliminary step in the process of dyeing.

Types of bleach

Household bleach, also known as *chlorine bleach*, sodium hypochlorite (NaClO), has a pH level of 11 and is used in the home for whitening clothes, removing stains, and disinfecting. This is because sodium hypochlorite yields chlorine radicals—oxidizing agents readily reacting with many substances.

Chlorine bleach is often used with laundry detergents and is also commonly used as a disinfectant. Mixing bleach and cleaners containing ammonia, or using bleach to clean up urine can create toxic chloramine gases and an explosive called nitrogen trichloride.

Hair bleach contains H2O2 (hydrogen peroxide), which gives off oxygen radicals as it decomposes. Oxygen and chlorine radicals both have comparable bleaching effects.

Various other peroxide yielding chemicals are used as bleaching additives. Sodium perborate, sodium percarbonate, sodium persulfate, sodium perphosphate, sodium persilicate, their ammonium, potassium and lithium analogs, calcium peroxide, zinc peroxide, sodium peroxide, carbamide peroxide, and others are commonly used in detergents, toothpastes, and other products.

Chlorine dioxide is used for the bleaching of wood pulp, fats and oils, cellulose, flour, textiles, beeswax, and in a number of other industries.

In the food industry, some organic peroxides (benzoyl peroxide, etc.) and other agents (e.g. bromates) are used as flour bleaching and maturing agents.

Not all bleaches have to be of oxidizing nature. Sodium dithionite is used as a powerful reducing agent in some bleaching formulas.

How bleaches work

Color in most dyes and pigments is produced by molecules, such as beta carotene, that contain moieties (pieces) known as chromophores. Chemical bleaches work in one of two ways:

- An oxidizing bleach works by breaking the chemical bonds that make up the chromophore. This changes the molecule into a different substance that either does not contain a chromophore, or contains a chromophore that does not absorb visible light.
- A reducing bleach works by converting double bonds in the chromophore into single bonds. This eliminates the ability of the chromophore to absorb visible light.[1]

Sunlight acts as a bleach through a process leading to similar results: high energy photons of light, often in the violet or ultraviolet range, can disrupt the bonds in the chromophore, rendering the resulting substance colorless. [2]

Hazards

A problem with chlorine is that it reacts with organic material to form trihalomethanes like chloroform, which is a well known carcinogen. There is debate over whether any risk from the chloroform in treated drinking water is worth the benefits. However, the use of elemental chlorine in industrial processes such as paper bleaching, with its attendant production of organochlorine-persistent organic pollutants (including dioxins), does not have any benefits. As a consequence over 80 % of the woodpulp is nowadays bleached with chlorine dioxide, reducing the dioxin generation under detectable levels.

Chlorine is a respiratory irritant. It also attacks mucus membranes and burns the skin. As little as 3.5 ppm can be detected as an odor, and 1000 ppm is likely to be fatal after a few deep breaths. Exposure to chlorine should not exceed 0.5 ppm (8-hour time-weighted average - 40 hour week).

Another hazard is the formation of acrid chloramine fumes when hypochlorite bleach comes into contact with ammonia or urine, which, though not nearly as dangerous as chlorine, can cause severe respiratory distress.

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E.R. Trotman. Textile Scouring and Bleaching. London: Charles Griffin & Co., 1968.

Dr. Bailey Bodkins. Bleach. Philedelphia: Virginia Printing Press 1995.

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- *1* Field, Simon Q (2006). Ingredients -- Bleach. Science Toys. Retrieved on 2006-03-02.
- 2 Bloomfield, Louis A (2006). Sunlight. How Things Work Home Page. Retrieved on 2006-03-02.

Chlorine dioxide

Molecular formula ClO_2

Molar mass 67.45 g/mol

CAS number [10049-04-4]

EINECS number 233-162-8

Density 3.09 g/l (gas), 1.642 g/cm^3 (liquid)

Solubility (water) Hydrolysis

Melting point 59°C

Boiling point 10°C

Thermodynamic data

Standard enthalpy of formation ”***f***H°***solid*** +104.60 kJ/mol

Standard molar entropy S°***solid*** 257.22 J K1 mol1

Heat capacity C***p*** 24.12 J K1 mol1

Safety data

EU classification

Oxidant (O)
Very toxic (T+)
Dangerous for the environment (N)

R-phrases R6, R8, R24, R36, R50

S-phrases S1/2, S23, S26, S28, S36/37/39, S38, S45, S61

Chlorine dioxide is a reddish-yellow gas which is one of several known oxides of chlorine. Chlorine dioxide is not stable in the gas state above 15% volume in air at STP (115 mm Hg) and can spontaneously and explosively decompose into chlorine and oxygen. Practically, it is never handled in its pure (concentrated) form. It is almost always used as a dissolved gas in water in a concentration range of 0.5 to 10 grams/liter. Chlorine dioxide is inversely soluble with temperature. In order to keep chlorine dioxide in solution, it is common to used chilled water (5°C or 41°F) when storing at concentrations above 3 grams/liter. In many countries, such as the USA, chlorine dioxide gas may not be transported at any concentration and is almost always produced at the application site using a chlorine dioxide generator. In some countries, chlorine dioxide solution below 3 grams/liter in concentration may be transported by land, but are relatively unstable and deteriorate quickly.

A number of products are marketed as "stabilized chlorine dioxide" (SCD). These are not actually solutions of chlorine dioxide but solutions of buffered sodium chlorite. A weak acid can be added to SCD to "activate" it and make chlorine dioxide in-situ without a chlorine dioxide generator. The use of SCD is effective when the demand for chlorine dioxide is low and when impurities, such as small amounts of chlorine, can be tolerated. For application requiring above 5 kg day1 ClO***2***, chlorine dioxide produced by a generator with either sodium chlorite or sodium chlorate is typically more economical.

Uses

Chlorine dioxide is used primarily (>95%) for bleaching of wood pulp, but is also used for the bleaching of flour and for the disinfection of water. The Niagara Falls, New York water treatment plant first used chlorine dioxide for drinking water treatment in 1944 for phenol destruction. Chlorine dioxide was introduced as a drinking water disinfectant on a large scale in 1956, when Brussels, Belgium, changed from chlorine to chlorine dioxide. Its most common use in water treatment is as a pre-oxidant prior to chlorination of drinking water to reduce trihalomethanes which are a carcinogenic disinfection by-product associated with chlorination of naturally occurring organics in the raw water. Chlorine dioxide is also used in conjunction with ozone disinfection of water to reduce the formation of bromates which are regulated carcinogens. Chlorine dioxide is also superior to chlorine when operating above neutral pH, when ammonia is present and for the control of biofilms. Chlorine dioxide is used in many industrial water treatment applications as a biocide including cooling towers, process water and food processing. Chlorine dioxide is less corrosive than chlorine and superior for the control of legionella bacteria.

It is more effective than chlorine against viruses, bacteria and protozoa – including the cysts of Giardia and the oocysts of Cryptosporidium.

It can also be used for air disinfection, and was the principal agent used in the decontamination of buildings in the United States after the 2001 anthrax attacks. Recently, after the disaster of Hurricane Katrina in New Orleans, Louisiana and the surrounding Gulf Coast, chlorine dioxide has been used to eradicate dangerous mold from houses inundated by water from massive flooding.

Chlorine dioxide is used as an oxidant for phenol destruction in waste water streams, control of zebra mussels in water intakes and for odor control in the air scrubbers of animal byproduct (rendering) plants.

Preparation

Chlorine dioxide can be produced with high efficiency by reducing sodium chlorate in a strong acid solution with a suitable reducing agent (for example, hydrogen peroxide, sulfur dioxide, or hydrochloric acid):

2ClO***3*** + 2Cl + 4H+ ’ 2ClO***2*** + Cl***2*** + 2H***2***O

Over 95% of the chlorine dioxide produced in the world today is made via the sodium chlorate method for pulp bleaching.

A much smaller but important market for chlorine dioxide is for use as a disinfectant. Since 1999 a growing proportion of the chlorine dioxide made globally for water treatment and other small scale applications has been made using the chlorate, hydrogen peroxide and sulfuric acid method which can produce a chlorine free product at high efficiency.

Traditionally, chlorine dioxide for disinfection applications has been made by one of three methods using sodium chlorite:

sodium chlorite - chlorine gas method:

$2NaClO_2 + Cl_2$ ’ $2ClO_2 + 2NaCl$

or the sodium chlorite - hypochlorite method:

$2NaClO_2 + 2HCl + NaOCl$ ’ $2ClO_2 + 3NaCl + H_2O$

or the sodium chlorite - hydrochloric acid method:

$5NaClO_2 + 4HCl$ ’ $5NaCl + 4ClO_2$

All three sodium chlorite chemistries can produce chlorine dioxide with high chlorite conversion yield, but the chlorite-HCl method suffers from the requirement of 25% more chlorite to produce an equivlent amount of chlorine dioxide.

Chlorine dioxide can also be produced by electrolysis of a chlorite solution:

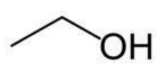
$2NaClO_2 + 2H_2O$ ’ $2ClO_2 + 2NaOH + H_2$

High purity chlorine dioxide gas (7.7% in air or nitrogen) can be produced by the Gas:Solid method, which reacts dilute chlorine gas with solid sodium chlorite.

$2NaClO_2 + Cl_2$ ’ $2ClO_2 + 2NaCl$

These processes and several slight variations are reviewed in Geo. Clifford White's Handbook of Chlorination and Alternative Disinfectants, 4th Edition (Wiley, 1999).

Ethanol



Systematic name Ethanol

Other names Ethyl alcohol, grain alcohol, hydroxyethane, EtOH

Molecular formula C_2H_6O

SMILES CCO

Molar mass 46.06844(232) g/mol

Appearance colourless clear liquid

CAS number [64-17-5]

Properties

Density and phase 0.789 g/cm^3, liquid

Solubility in water Fully miscible

Melting point 114.3 °C (158.8 K)

Boiling point 78.4 °C (351.6 K)

Acidity (p*Ka*) 15.9 (H± from OH group)

Viscosity 1.200 cP at 20 °C

Dipole moment 1.69 D (gas)

Hazards

MSDS External MSDS

EU classification Flammable (*F*)
R-phrases **R11**

S-phrases **S2**, **S7**, **S16**

Flash point 13 °C (55.4 °F)

RTECS number KQ6300000

Related compounds

Related alcohols Methanol, 1-Propanol

Other heteroatoms Ethylamine, Ethyl chloride, Ethyl bromide, Ethanethiol

Substituted ethanols Ethylene glycol, Ethanolamine, 2-Chloroethanol

Other compounds Acetaldehyde, Acetic acid

Except where noted otherwise, data are given for materials in their standard state (at 25°C, 100 kPa)

Ethanol, also known as *ethyl alcohol* or grain alcohol, is a flammable, colorless, mildly toxic chemical compound with a distinctive perfume-like odor, and is the alcohol found in alcoholic beverages. In common usage, it is often referred to simply as alcohol. Its molecular formula is variously represented as EtOH, C2H5OH or as its empirical formula C2H6O.

History

Ethanol has been used by humans since prehistory as the intoxicating ingredient in alcoholic beverages. Dried residues on 9000-year-old pottery found in northern mainland China imply the use of alcoholic beverages even among Neolithic peoples.[1] Its isolation as a relatively pure compound was first achieved by Persian alchemists who developed the art of distillation during the Abbasid caliphate, the most notable of whom was Al-Razi. The writings attributed to Jabir Ibn Hayyan (Geber) (721-815) mention the flammable vapors of boiled wine. Al-Kind+ (801-873) unambiguously described the distillation of wine.[2] Distillation of ethanol from water yields a product that is at most 95.6% ethanol, because ethanol forms an azeotrope with water. Absolute ethanol was first obtained in 1796 by Johann Tobias Lowitz, by filtering distilled ethanol through charcoal.

Antoine Lavoisier described ethanol as a compound of carbon, hydrogen, and oxygen, and in 1808, Nicolas-Théodore de Saussure determined ethanol's chemical formula, and fifty years later, in 1858, Archibald Scott Couper published a structural formula for ethanol: this places ethanol among the first chemical compounds to have their chemical structures determined.[3]

Ethanol was first prepared synthetically in 1826, through the independent efforts of Henry Hennel in Great Britain and S.G. Sérullas in France. Michael Faraday prepared ethanol by the acid-catalysed hydration of ethylene in 1828, in a process similar to that used for industrial ethanol synthesis today.[4]

Ethanol served as lamp fuel in pre-Civil War United States and helped power early Model T automobiles. But the fuel couldn't compete with the low cost and availability of petroleum, and ethanol faded from the public eye. The recent rise in oil prices has spurred renewed interest.[5]

Physical properties

Ethanol's hydroxyl group is able to participate in hydrogen bonding. At the molecular level, liquid ethanol consists of hydrogen-bonded pairs of ethanol molecules; this phenomenon renders ethanol more viscous and less volatile than less polar organic compounds of similar molecular weight. In the vapor phase, there is little hydrogen bonding; ethanol vapor consists of individual ethanol molecules.

Ethanol has a refractive index of 1.3614.

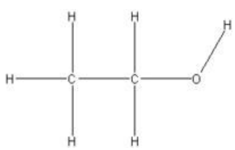
Ethanol is a versatile solvent. It is miscible with water and with most organic liquids, including nonpolar liquids such as aliphatic hydrocarbons. Organic solids of low molecular weight are usually soluble in ethanol. Among ionic compounds, many monovalent salts are at least somewhat soluble in ethanol, with salts of large, polarizable ions being more soluble than salts of smaller ions. Most salts of polyvalent ions are practically insoluble in ethanol.

Furthermore, ethanol is used as a solvent in dissolving medicines, food flavourings and colourings that do not dissolve easily in water. Once the non-polar material is dissolved in the ethanol, water can be added to prepare a solution that is mostly water. The ethanol molecule has a water-loving (hydrophilic) -OH group that helps it dissolve polar molecules and ionic substances. The short, water-fearing (hydrophobic) hydrocarbon chain CH_3CH_2-

can attract non-polar molecules. Thus ethanol can dissolve both polar and non-polar substances.

Several unusual phenomena are associated with mixtures of ethanol and water. Ethanol-water mixtures have less volume than their individual components: a mixture of equal volumes ethanol and water has only 95.6% of the volume of equal parts ethanol and water, unmixed. The addition of even a few percent of ethanol to water sharply reduces the surface tension of water. This property partially explains the tears of wine phenomenon: when wine is swirled inside a glass, ethanol evaporates quickly from the thin film of wine on the wall of the glass. As its ethanol content decreases, its surface tension increases, and the thin film beads up and runs down the glass in channels rather than as a smooth sheet.

Chemistry



Chemical formula of ethanol, (C is carbon, the dash is a single bond, H is hydrogen, O is oxygen)

The chemistry of ethanol is largely that of its hydroxyl group.

Acid-base chemistry

Ethanol's hydroxyl proton is very weakly acidic; it is an even weaker acid than water. Ethanol can be quantitatively converted to its conjugate base, the ethoxide ion (CH3CH2O), by reaction with an alkali metal such as sodium. This reaction evolves hydrogen gas:

$2CH_3CH_2OH + 2Na$ ’ $2CH_3CH_2ONa + H_2$

Nucleophilic substitution

In aprotic solvents, ethanol reacts with hydrogen halides to produce ethyl halides such as ethyl chloride and ethyl bromide via nucleophilic substitution:

$CH_3CH_2OH + HCl$ ’ $CH_3CH_2Cl + H_2O$ $CH_3CH_2OH + HBr$ ’ $CH_3CH_2Br + H_2O$

Ethyl halides can also be produced by reacting ethanol by more specialized halogenating agents, such as thionyl chloride for preparing ethyl chloride, or phosphorus tribromide for preparing ethyl bromide.

Esterification

Under acid-catalysed conditions, ethanol reacts with carboxylic acids to produce ethyl esters and water:

$RCOOH + HOCH_2CH_3$ ’ $RCOOCH_2CH_3 + H_2O$

The reverse reaction, hydrolysis of the resulting ester back to ethanol and the carboxylic acid, limits the extent of reaction, and high yields are unusual unless water can be removed from the reaction mixture as it is formed. Esterification can also be carried out using more a reactive derivative of the carboxylic acid, such as an acyl chloride or acid anhydride.

Ethanol can also form esters with inorganic acids. Diethyl sulfate and triethyl phosphate, prepared by reacting ethanol with sulfuric and phosphoric acid, respectively, are both useful ethylating agents in organic synthesis. Ethyl nitrite, prepared from the reaction of ethanol with sodium nitrite and sulfuric acid, was formerly a widely-used diuretic.

Dehydration

Strong acids, such as sulfuric acid, can catalyse ethanol's dehydration to form either diethyl ether or ethylene:

2 CH_3CH_2OH ’ $CH_3CH_2OCH_2CH_3 + H_2O$ CH_3CH_2OH ’ $H_2C=CH_2 + H_2O$

Which product, diethyl ether or ethylene, predominates depends on the precise reaction conditions.

Oxidation

Ethanol can be oxidized to acetaldehyde, and further oxidized to acetic acid. In the human body, these oxidation reactions are catalysed by enzymes. In the laboratory, aqueous solutions of strong oxidizing agents, such as chromic acid or potassium permanganate, oxidize ethanol to acetic acid, and it is difficult to stop the reaction at acetaldehyde at high yield. Ethanol can be oxidized to acetaldehyde, without overoxidation to acetic acid, by reacting it with pyridinium chromic chloride.

Combustion

Combustion of ethanol forms carbon dioxide and water:

$C_2H_5OH + 3\ O_2$ ’ $2\ CO_2 + 3\ H_2O$

Production

Ethanol is produced both as a petrochemical, through the hydration of ethylene, and biologically, by fermenting sugars with yeast.

Ethylene hydration

Ethanol for use as industrial feedstock is most often made from petrochemical feedstocks, typically by the acid-catalyzed hydration of ethene, represented by the chemical equation

C2H4 + H2O ’ CH3CH2OH

The catalyst is most commonly phosphoric acid, adsorbed onto a porous support such as diatomaceous earth or charcoal; this catalyst was first used for large-scale ethanol production by the Shell Oil Company in 1947.[6] Solid catalysts, mostly various metal oxides, have also been mentioned in the chemical literature.

In an older process, first practiced on the industrial scale in 1930 by Union Carbide,[7] but now almost entirely obsolete, ethene was hydrated indirectly by reacting it with concentrated sulfuric acid to product ethyl sulfate, which was then hydrolysed to yield ethanol and regenerate the sulfuric acid:

C2H4 + H2SO4 ’ CH3CH2SO4H CH3CH2SO4H + H2O ’ CH3CH2OH + H2SO4

Fermentation

Ethanol for use in alcoholic beverages, and the vast majority of ethanol for use as fuel, is produced by fermentation: when certain species of yeast (most importantly, Saccharomyces cerevisiae) metabolize sugar in the absence of oxygen, they produce ethanol and carbon dioxide. The overall chemical reaction conducted by the yeast may be represented by the chemical equation

C6H12O6 ’ 2 CH3CH2OH + 2 CO2

The process of culturing yeast under conditions to produce alcohol is referred to as brewing. Brewing can only produce relatively dilute concentrations of ethanol in water; concentrated ethanol solutions are toxic to yeast. The most ethanol-tolerant strains of yeast can survive in up to about 25% ethanol (by volume).

During the fermentation process, it is important to prevent oxygen getting to the ethanol, since otherwise the ethanol would be oxidised to acetic acid (vinegar). Also, in the presence of oxygen, the yeast would undergo aerobic respiration to produce just carbon dioxide and water, without producing ethanol.

In order to produce ethanol from starchy materials such as cereal grains, the starch must first be broken down into sugars. In brewing beer, this has traditionally been accomplished allowing the grain to germinate, or malt. In the process of germination, the seed produces enzymes that can break its starches into sugars. For fuel ethanol, this hydrolysis of starch into glucose is accomplished more rapidly by treatment with dilute sulfuric acid, fungal amylase enzymes, or some combination of the two.

At petroleum prices like those that prevailed through much of the 1990s, ethylene hydration was a decidedly more economical process than fermentation for producing purified ethanol. Recent increases in petroleum prices, coupled with perennial uncertainty in agricultural prices, make forecasting the relative production costs of fermented versus petrochemical ethanol difficult at the present time.

Purification

The product of either ethylene hydration or brewing is an ethanol-water mixture. For most industrial and fuel uses, the ethanol must be purified. Fractional distillation can concentrate ethanol to 95.6% volume; the mixture of 95.6% ethanol and 4.4% water (percentage by weight) is an azeotrope with a boiling point of 78.2 °C, and cannot be further purified by distillation. Therefore, 95% ethanol in water is a fairly common solvent.

After distillation ethanol can be further purified by "drying" it using lime or salt. Lime, (calcium oxide), when mixed with the water in ethanol will form calcium hydroxide, which then can be separated. Dry salt will dissolve some of the water content of the ethanol as it passes through, leaving a purer alcohol.[8]

Several approaches are used to produce absolute ethanol. The ethanol-water azeotrope can be broken by the addition of a small quantity of benzene. Benzene, ethanol, and water form a ternary azeotrope with a boiling point of 64.9 °C. Since this azeotrope is more volatile than the ethanol-water azeotrope, it can be fractionally distilled out of the ethanol-water mixture, extracting essentially all of the water in the process. The bottoms from such a distillation is anhydrous ethanol, with several parts per million residual benzene. Benzene is toxic to humans, and cyclohexane has largely supplanted benzene in its role as the entrainer in this process.

Alternatively, a molecular sieve can be used to selectively absorb the water from the 95.6% ethanol solution. Synthetic zeolite in pellet form can be used, as well as a variety of plant-derived absorbents, including cornmeal, straw, and sawdust. The zeolite bed can be regenerated essentially an unlimited number of times by drying it with a blast of hot carbon dioxide. Cornmeal and other plant-derived absorbents cannot readily be regenerated, but where ethanol is made from grain, they are often available at low cost. Absolute ethanol produced this way has no residual benzene, and can be used as fuel, or, when diluted, can even be used to fortify port and sherry in traditional winery operations.

At pressures less than atmospheric pressure, the composition of the ethanol-water azeotrope shifts to more ethanol-rich mixtures, and at pressures less than 70 torr (9.333 kPa) , there is no azeotrope, and it is possible to distill absolute ethanol from an ethanol-water mixture. While vacuum distillation of ethanol is not presently economical, pressure-swing distillation is a topic of current research. In this technique, a reduced-pressure distillation first yields an ethanol-water mixture of more than 95.6% ethanol. Then, fractional distillation of this mixture at atmospheric pressure distills off the 95.6% azeotrope, leaving anhydrous ethanol at the bottoms.

Prospective technologies

Glucose for fermentation into ethanol can also be obtained from cellulose. Until recently, however, the cost of the cellulase enzymes that could hydrolyse cellulose has been prohibitive. The Canadian firm Iogen brought the first cellulose-based ethanol plant on-stream in 2004.[9] The primary consumer thus far has been the Canadian government, which, along with the United States government (particularly the Department of Energy's National Renewable Energy Laboratory), has invested millions of dollars into assisting the commercialization of cellulosic ethanol. Realization of this technology would turn a number of cellulose-containing agricultural byproducts, such as corncobs, straw, and sawdust, into renewable energy resources.

Cellulosic materials typically contain, in addition to cellulose, other polysaccharides, including hemicellulose. When hydrolysed, hemicellulose breaks down into mostly five-carbon sugars such as xylose. S. cerevisiae, the yeast most commonly used for ethanol production, cannot metabolize xylose. Other yeasts and bacteria are under investigation to metabolize xylose and so improve the ethanol yield from cellulosic material.[10][11]

The anaerobic bacterium Clostridium ljungdahlii, recently discovered in commercial chicken wastes, can produce ethanol from single-carbon sources including synthesis gas, a mixture of carbon monoxide and hydrogen that can be generated from the partial

combustion of either fossil fuels or biomass. Use of these bacteria to produce ethanol from synthesis gas has progressed to the pilot plant stage at the BRI Energy facility in Fayetteville, Arkansas;[12] in the BRI process, the heat released by gasification can be used to co-produce electricity with ethanol.

Another prospective technology is the closed-loop ethanol plant. Ethanol produced from corn has a number of critics who suggest that it is primarily just recycled fossil fuels because of the energy required to grow the grain and convert it into ethanol. However, the closed-loop ethanol plant attempts to address this criticism. In a closed-loop plant, the energy for the distillation comes from fermented manure, produced from cattle that have been fed the by-products from the distillation. The leftover manure is then used to fertilize the soil used to grow the grain. Such a process is expected to have a much lower fossil fuel requirement.[13]

Ethanol

Denatured alcohol

In most jurisdictions, the sale of ethanol, as a pure substance, or in the form of alcoholic beverages, is heavily taxed. In order to relieve non-beverage industries of this tax burden, governments specify formulations for denatured alcohol, which consists of ethanol blended with various additives to render it unfit for human consumption. These additives, called denaturants, are generally either toxic (such as methanol) or have unpleasant tastes or odors (such as denatonium benzoate).

Specialty denatured alcohols are denatured alcohol formulations intended for a particular industrial use, containing denaturants chosen so as not to interfere with that use. While they are not taxed, purchasers of specialty denatured alcohols must have a government-issued permit for the particular formulation they use and must comply with other regulations.

Completely denatured alcohols are formulations that can be purchased for any legal purpose, without permit, bond, or other regulatory compliance. It is intended that it be difficult to isolate a product fit for human consumption from completely denatured alcohol. For example, the completely denatured alcohol formulation used in the United Kingdom contains (by volume) 89.66% ethanol, 9.46% methanol, 0.50% pyridine, 0.38% naphtha, and is dyed purple with methyl violet.[14]

Hydrous and anhydrous ethanol

Hydrous and anhydrous ethanol are terms used to describe ethanol by the type of process used to covert biomass into fuel. There are different prices for each anhydrous and hydrous ethanol depending on market demands.

The term hydrous pyrolysis is sometimes used to encompass thermolysis in the presence of water, such as steam cracking of oil, or more generally hydrous pyrolysis. An example of the latter is thermal depolymerization of organic waste into light crude oil.

Anhydrous (without water) pyrolysis can be used to produce liquid fuel similar to diesel from solid biomass. The most common technique uses very low residence times (<2 seconds) and high heating rates using a temperature between 350-500 °C. It is called either fast or flash pyrolysis.'

Anhydrous Alcohol can also be produced from hydrous(95-96%) alcohol using drying agents like molecular sieves, or by azeotropic distillation, extractive distillation techniques.

Absolute ethanol

Absolute or anhydrous alcohol generally refers to purified ethanol, containing no more than one percent water.

It is not possible to obtain absolute alcohol by simple fractional distillation, because a mixture containing around 95.6% alcohol and 4.4% water becomes a constant boiling mixture (an azeotropic mixture). In one common industrial method to obtain 100% pure alcohol, a small quantity of benzene is added to rectified spirit and the mixture is then distilled. Absolute alcohol is obtained in third fraction that distills over at 78.2 °C (351.3 K).

Because a small amount of the benzene used remains in the solution, absolute alcohol produced by this method is not suitable for consumption as benzene is carcinogenic.

There is also an absolute alcohol production process by desiccation using glycerol. Alcohol produced by this method is known as spectroscopic alcohol - so called because the absence of benzene makes it suitable as a solvent in spectroscopy.

Currently, the most popular method of purification past 95.6% purity is desiccation using adsorbents such as starch or zeolites. These adsorb water preferentially.

Feedstocks

Currently the main feedstock in the United States for the production of ethanol is corn (see the Renewable Fuels Association's list of U.S. ethanol for a complete list and feedstock utilized[1]).

Trials of a new crop, switchgrass, are showing much greater yields.

The dominant ethanol feedstock in warmer regions is sugarcane.

In some parts of Europe, particularly France and Italy, wine is used as a feedstock due to massive oversupply.

Use

As a fuel

The largest single use of ethanol is as a motor fuel and fuel additive. The largest national fuel ethanol industries exist in Brazil (all fuel sold in Brazil contains at least 20% ethanol).[15] One method of production is through fermentation of sugar. Ethanol creates very little pollution when being burned.However, the production process is actually more detrimental to the environment. Millions more acres of land are needed if ethanol is to be used to replace gasoline. It has a lower energy content than gasoline.[16][17] At gas stations,

ethanol is contained in a mix of ethanol and gasoline, otherwise known as gasahol. In the United States, the color yellow (symbolizing the color of corn) has become associated with the fuel and is commonly used on fuel pumps and labels.

Alcoholic beverages

Alcoholic beverages vary considerably in their ethanol content and in the foodstuffs from which they are produced. Most alcoholic beverages can be broadly classified as fermented beverages, beverages made by the action of yeast on sugary foodstuffs, or as distilled beverages, beverages whose preparation involves concentrating the ethanol in fermented beverages by distillation. The ethanol content of a beverage is usually measured in terms of the volume fraction of ethanol in the beverage, expressed either as a percentage or in alcoholic proof units.

Fermented beverages can be broadly classified by the foodstuff from which they are fermented. Beers are made from cereal grains or other starchy materials, wines and ciders from fruit juices, and meads from honey. Cultures around the world have made fermented beverages from numerous other foodstuffs, and local and national names for various fermented beverages abound. Fermented beverages may contain up to 15–20% ethanol by volume, the upper limit being set by the yeast's tolerance for ethanol, or by the amount of sugar in the starting material.

Distilled beverages are made by distilling fermented beverages. Broad categories of distilled beverages include whiskies, distilled from fermented cereal grains; brandies, distilled from fermented fruit juices, and rum, distilled from fermented molasses or sugarcane juice. Vodka and similar neutral grain spirits can be distilled from any fermented material (grain or potatoes is most common); these spirits are so thoroughly distilled that no tastes from the particular starting material remain. Numerous other spirits and liqueurs are prepared by infusing flavors from fruits, herbs, and spices into distilled spirits. A traditional example is gin, the infusion of juniper berries into neutral grain alcohol.

In a few beverages, ethanol is concentrated by means other than distillation. Applejack is traditionally made by freeze distillation: water is frozen out of fermented apple cider, leaving a more ethanol-rich liquid behind. Fortified wines are prepared by adding brandy or some other distilled spirit to partially-fermented wine. This kills the yeast and conserves some of the sugar in grape juice; such beverages are not only more ethanol-rich, but also sweeter than other wines.

Chemicals derived from ethanol

Ethyl esters

In the presence of an acid catalyst (typically sulfuric acid) ethanol reacts with carboxylic acids to produce ethyl esters:

CH*3*CH*2*OH + RCOOH ’ RCOOCH*2*CH*3* + H*2*O

The two largest-volume ethyl esters are ethyl acrylate (from ethanol and acrylic acid) and ethyl acetate (from ethanol and acetic acid). Ethyl acrylate is a monomer used to prepare acrylate polymers for use in coatings and adhesives. Ethyl acetate is a common solvent used in paints, coatings, and in the pharmaceutical industry; its most familiar application in the household is as a solvent for nail polish. A variety of other ethyl esters are used in much smaller volumes as artificial fruit flavorings.

Vinegar

Vinegar is a dilute solution of acetic acid prepared by the action of Acetobacter bacteria on ethanol solutions. Although traditionally prepared from alcoholic beverages including wine, apple cider, and unhopped beer, vinegar can also be made from solutions of industrial ethanol. Vinegar made from distilled ethanol is called "distilled vinegar", and is commonly used in food pickling and as a condiment.

Ethylamines

When heated to 150–220 °C over a silica- or alumina-supported nickel catalyst, ethanol and ammonia react to produce ethylamine. Further reaction leads to diethylamine and triethylamine:

- CH3CH2OH + NH3 ’ CH3CH2NH2 + H2O

CH3CH2OH + CH3CH2NH2 ’ (CH3CH2)2NH + H2O

CH3CH2OH + (CH3CH2)2NH ’ (CH3CH2)3N + H2O

The ethylamines find use in the synthesis of pharmaceuticals, agricultural chemicals, and surfactants.

Other chemicals

Ethanol is cool, and in the past has been used commercially to synthesize dozens of other high-volume chemical commodities. At the present, it has been supplanted in many applications by less costly petrochemical feedstocks. However, in markets with abundant agricultural products, but a less developed petrochemical infrastructure, such as the People's Republic of China, Pakistan, India, and Brazil, ethanol can be used to produce chemicals that would be produced from petroleum in the West, including ethylene and butadiene.

Other uses

Ethanol is easily soluble in water in all proportions with a slight overall decrease in volume when the two are mixed. Absolute ethanol and 95% ethanol are themselves good solvents, somewhat less polar than water and used in perfumes, paints and tinctures. Other proportions of ethanol with water or other solvents can also be used as a solvent. Alcoholic drinks have a large variety of tastes because various flavor compounds are dissolved during brewing. When ethanol is produced as a mixing beverage it is a neutral grain spirit.

Ethanol is used in medical wipes and in most common antibacterial hand sanitizer gels at a concentration of about 62% (percentage by weight, not volume) as an antiseptic. The peak of the disinfecting power occurs around 70% ethanol; stronger and weaker solutions of ethanol have a lessened ability to disinfect. Solutions of this strength are often used in laboratories for disinfecting work surfaces. Ethanol kills organisms by denaturing their proteins and dissolving their lipids and is effective against most bacteria and fungi, and many viruses, but is ineffective against bacterial spores. Alcohol does not act like an antibiotic and

is not effective against infections by ingestion. Ethanol in the low concentrations typically found in most alcoholic beverages does not have useful disinfectant or antiseptic properties, internally or externally.

Wine with less than 16% ethanol cannot protect itself against bacteria. Because of this, port is often fortified with ethanol to at least 18% ethanol by volume to halt fermentation for retaining sweetness and in preparation for aging, at which point it becomes possible to prevent the invasion of bacteria into the port, and to store the port for long periods of time in wooden containers that can 'breathe', thereby permitting the port to age safely without spoiling. Because of ethanol's disinfectant property, alcoholic beverages of 18% ethanol or more by volume can be safely stored for a very long time.

Metabolism and toxicology

Pure ethanol is a tasteless liquid with a strong and distinctive odor that produces a characteristic heat-like sensation when brought into contact with the tongue or mucous membranes. When applied to open wounds (as for disinfection) it produces a strong stinging sensation. Pure or highly concentrated ethanol may permanently damage living tissue on contact. Ethanol applied to unbroken skin cools the skin rapidly through evaporation.

In the human body, ethanol is first oxidized to acetaldehyde, and then to acetic acid. The first step is catalysed by the enzyme alcohol dehydrogenase, and the second by acetaldehyde dehydrogenase. Some individuals have less effective forms of one or both of these enzymes, and can experience more severe symptoms from ethanol consumption than others. Conversely, those who have acquired ethanol tolerance have a greater quantity of these enzymes, and metabolize ethanol more rapidly.

BAC (mg/dL), Symptoms

50: Euphoria, talkativeness, relaxation

100: Central nervous system depression, impaired motor and sensory function, impaired cognition

>140: Decreased blood flow to brain

300: Stupefaction, possible unconsciousness

400: Possible death

>550: Death highly likely[18]

The amount of ethanol in the body is typically quanitified by blood alcohol content (BAC), the milligrams of ethanol per 100 milliliters of blood. The table at right summarizes the symptoms of ethanol consumption. Small doses of ethanol generally produce euphoria and relaxation; people experiencing these symptoms tend to become talkative and less inhibited, and may exhibit poor judgment. At higher dosages (BAC > 0.10), ethanol acts as a central

nervous system depressant, producing at progressively higher dosages, impaired sensory and motor function, slowed cognition, stupefaction, unconsciousness, and possible death.

The initial product of ethanol metabolism, acetaldehyde, is more toxic than ethanol itself. The body can quickly detoxify some acetaldehyde by reaction with glutathione and similar thiol-containing biomolecules. When acetaldehyde is produced beyond the capacity of the body's glutathione supply to detoxify it, it accumulates in the bloodstream until further oxidized to acetic acid. The headache, nausea, and malaise associated with an alcohol hangover stem from a combination of dehydration and acetaldehyde poisoning; many health conditions associated with chronic ethanol abuse, including liver cirrhosis, alcoholism, and some forms of cancer, have been linked to acetaldehyde.[citation needed] The judicial system in the United States, in a number of jurisdictions, promoted the use of disulfiram, known as Antabuse, for persons convicted of driving while (alcohol) intoxicated. Disulfuram interferes with hepatic acetaldehyde metabolism, exacerbating the discomforts noted above. Numerous deaths, said to be related to disulfuram use, led to the elimination of these court-based programs. Some medications, including paracetamol (acetaminophen), as well as exposure to organochlorides, can deplete the body's glutathione supply, enhancing both the acute and long-term risks of even moderate ethanol consumption. Frequent use of alcoholic beverages has also been shown to be a major contributing factor in cases of elevated blood levels of triglycerides. [2]

Ethanol has been shown to increase the growth of Acinetobacter baumannii, a bacterium responsible for pneumonia, meningitis and urinary tract infections. This finding may contradict the common misconception that drinking alcohol could kill off a budding infection. (Smith and Snyder, 2005)

Hazards

- Ethanol-water solutions greater than about 50% ethanol by volume are flammable and easily ignited. Ethanol-water solutions below 50% ethanol by volume may also be flammable if the solution is vaporized by heating (as in some cooking methods that call for wine to be added to a hot pan, causing it to flash boil into a vapor, which is then ignited to "burn off" excessive alcohol).

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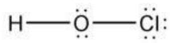
Hypochlorous acid



Systematic name hypochlorous acid

Molecular formula HClO

Molar mass 52.46 g/mol

Appearance colorless aqueous solns

CAS number [7790-92-3]

Properties

Solubility in water soluble

Other solvents Et2O, CH2Cl2

Acidity (pK***a***) 7.53

Hazards

MSDS External MSDS

Main hazards oxidizer

Related compounds

Other anions NaOCl

Other cations HOBr, HOF

Related compounds Cl***2,*** Ca(OCl)$_2$

Except where noted otherwise, data are given for materials in their standard state (at 25 °C, 100 kPa)

Hypochlorous acid is a weak acid with the chemical formula HOCl. It forms when chlorine dissolves in water. It cannot be isolated in pure form due to rapid equilibration with its precursor (see below). HOCl is used as a bleach, an oxidizer, a deodorant, and a disinfectant.

Formation

Addition of chlorine to water gives both hypochlorous acid and hydrochloric acid (HCl):

$Cl_2 + H_2O$ ’ $HClO + HCl$

Chemical reactions

In aqueous solution, hypochlorous acid partially dissociates into the *hypochlorite anion* ClO^- (also known as the *chlorate(I) anion*) and the proton H^+. The salts of hypochlorous acid are also called *hypochlorites*. One of the best known hypochlorites is household bleach, sodium hypochlorite, NaClO.

In the presence of sunlight, hypochlorous acid decomposes into more hydrochloric acid and oxygen, so this reaction is sometimes seen as:

$2Cl_2 + 2H_2O$ ’ $4HCl + O_2$

HClO is considered to be a stronger oxidant than chlorine.

Uses

In organic synthesis, HOCl converts alkenes to chlorohydrins.[1]

In biology, hypochlorous acid is thought to be produced by neutrophils to kill bacteria, and it is the active sanitizer in all chlorine-based swimming pool products.

Safety

HOCl is a strong oxidant and thus can form explosive mixtures, and it can give off toxic chlorine gas.

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Ozone

Systematic name Trioxygen

Molecular formula O_3

Molar mass 47.998 g/mol

Appearance bluish colored gas

CAS number [10028-15-6]

Properties

Density and phase 2.144 g/l (0 °C), gas

Solubility in water 0.105 g/100 ml (0 °C)

Melting point 80.7 K, 192.5 °C

Boiling point 161.3 K, 111.9 °C

Thermodynamic data

Standard enthalpy of formation ”***f***H°***solid*** +142.3 kJ/mol

Standard molar entropy S°***solid*** 237.7 J.K**1**.mol**1**

Hazards

EU classification not listed

NFPA 704

Except where noted otherwise, data are given for materials in their standard state (at 25 °C, 100 kPa)

Ozone (*O*3) is a triatomic molecule, consisting of three oxygen atoms. It is an allotrope of oxygen that is much less stable than the diatomic species O2. It is present in low concentrations throughout the Earth's atmosphere. It has many industrial and consumer applications as well as being used in ozone therapy.

Ozone, the first allotrope of a chemical element to be described by science, was discovered by Christian Friedrich Schönbein in 1840, who named it after the Greek word for smell (ozein), from the peculiar odor in lightning storms.[1] The odor from a lightning strike is from electrons freed during the rapid chemical changes, not the ozone itself.[2]

Physical properties

Undiluted ozone is a pale blue gas at standard temperature and pressure; it forms a dark blue liquid below 112 °C and a violet-black solid below 193 °C [3]. At concentrations found in the atmosphere it is colorless [4]. The concentration above which it can be smelt (odor threshold) is between 0.0076 and 0.036 ppm[5].

Chemistry

Ozone is a powerful oxidizing agent. It is also unstable at high concentrations, decaying to ordinary diatomic oxygen:

$2\ O_3$ ’ $3\ O_2$.

This reaction proceeds more rapidly with increasing temperature and decreasing pressure. Ozone will oxidize metals (except gold, platinum, and iridium) to oxides of the metals in their highest oxidation state:

$2\ Cu^{2+} + 2\ H^{+} + O_3$ ’ $2\ Cu^{3+} + H_2O + O_2$

Ozone converts oxides to peroxides:

$SO_2 + O_3$ ’ $SO_3 + O_2$

It also increases the oxidation number of oxides:

$NO + O_3$ ’ $NO_2 + O_2$

The above reaction is accompanied by chemiluminescence. The NO_2 can be further oxidized:

$NO_2 + O_3$ ’ $NO_3 + O_2$

The NO_3 formed can react with NO_2 to form N_2O_5:

$NO_2 + NO_3$ ’ N_2O_5

Ozone reacts with carbon to form carbon dioxide, even at room temperature:

$C + 2\ O_3$ ’ $CO_2 + 2\ O_2$

Ozone does not react with ammonium salts but it reacts with ammonia to form ammonium nitrate:

$2\ NH_3 + 4\ O_3$ ’ $NH_4NO_3 + 4\ O_2 + H_2O$

Ozone reacts with sulfides to make sulfates:

$PbS + 4\ O_3$ ’ $PbSO_4 + 4\ O_2$

Sulfuric acid can be produced from ozone, either starting from elemental sulfur or from sulfur dioxide:

$S + H_2O + O_3$ ’ H_2SO_4 $3\ SO_2 + 3\ H_2O + O_3$ ’ $3\ H_2SO_4$

All three atoms of ozone may also react, as in the reaction with tin(II) chloride and hydrochloric acid:

$3\ SnCl_2 + 6\ HCl + O_3$ ’ $3\ SnCl_4 + 3\ H_2O$

In the gas phase, ozone reacts with hydrogen sulfide to form sulfur dioxide:

$H_2S + O_3$ ’ $SO_2 + H_2O$

In an aqueous solution, however, two competing simultaneous reactions occur, one to produce elemental sulfur, and one to produce sulfuric acid:

$H_2S + O_3$ ’ $S + O_2 + H_2O$ $3\ H_2S + 4\ O_3$ ’ $3\ H_2SO_4$

Iodine perchlorate can be made by treating iodine dissolved in cold anhydrous perchloric acid with ozone:

$I_2 + 6\ HClO_4 + O_3$ ’ $2\ I(ClO_4)_3 + 3\ H_2O$

Solid nitryl perchlorate can be made from NO_2, ClO_2, and O_3 gases:

$2\ NO_2 + 2\ ClO_2\ 2\ O_3$ ’ $2\ NO_2ClO_4 + O_2$

Ozone can be used for combustion reactions and combusting gases in ozone provides higher temperatures than combusting in dioxygen (O2). Following is a reaction for the combustion of carbon subnitride:

$3\ C_4N_2 + 4\ O_3$ ’ $12\ CO + 3\ N_2$

Ozone can react at cryogenic temperatures. At 77 K (-196 °C), atomic hydrogen reacts with liquid ozone to form a hydrogen superoxide radical, which dimerizes[6]

$H + O_3$ ’ $HO_2 + O$ $2\ HO_2$ ’ H_2O_4

Ozonides can be formed, which contain the ozonide anion, O3-. These compounds are explosive and must be stored at cryogenic temperatures. Ozonides for all the alkali metals are known. KO_3, RbO_3, and CsO_3 can be prepared from their respective superoxides:

$KO_2 + O_3$ ’ $KO_3 + O_2$

Although KO_3 can be formed as above, it can also be formed from potassium hydroxide and ozone:[7]

$2\ KOH + 5\ O_3$ ’ $2\ KO_3 + 5\ O_2 + H_2O$

NaO_3 and LiO_3 must be prepared by action of CsO_3 in liquid NH_3 on an ion exchange resin containing Na± or Li± ions:[8]

CsO_3 + Na± ’ Cs± + NaO_3

Treatment with ozone of calcium dissolved in ammonia leads to ammonium ozonide and not calcium ozonide:[9]

3 Ca + 10 NH*3* + 6 O*3* ' Ca•6NH*3* + Ca(OH)*2* + Ca(NO*3*)*2* + 2 NH*4*O*3* + 2 O*2* + H*2*

Ozone can be used to remove manganese from the water, forming a precipitate which can be filtered:

2 Mn2+ + 2 O*3* + 4 H*2*O ' 2 MnO(OH)*2* *(s)* + 2 O*2* + 4 H+

Ozone will also turn cyanides to the one thousand times less toxic cyanates:

CN- + O*3* ' CNO- + O*2*

Finally, ozone will also completely decompose urea:[10]

(NH*2*)*2*CO + O*3* ' N*2* + CO*2* + 2 H*2*O

Ozone in Earth's atmosphere

The standard way to express total ozone amounts (the amount of ozone in a vertical column) in the atmosphere is by using Dobson units. Concentrations at a point are measured in parts per billion (ppb) or in ¼g/m^3.

Ozone layer

The highest levels of ozone in the atmosphere are in the stratosphere, in a region also known as the ozone layer between about 10 km and 50 km above the surface. Here it filters out the shorter wavelengths (less than 320 nm) of ultraviolet light (270 to 400 nm) from the Sun that would be harmful to most forms of life in large doses. These same wavelengths are also responsible for the production of vitamin D, which is essential for human health. Ozone in the stratosphere is mostly produced from ultraviolet rays reacting with oxygen:

O*2* + (radiation < 240 nm) ' 2 O O + O*2* ' O*3*

It is destroyed by the reaction with atomic oxygen:

O*3* + O ' 2 O*2*

The latter reaction is catalysed by the presence of certain free radicals, of which the most important are hydroxyl (OH), nitric oxide (NO) and atomic chlorine (Cl) and bromine (Br). In recent decades the amount of ozone in the stratosphere has been declining mostly due to emissions of CFCs and similar chlorinated and brominated organic molecules, which have increased the concentration of ozone-depleting catalysts above the natural background. For more information on stratospheric ozone see Seinfeld and Pandis (1999).

Low level ozone

Low level ozone (or tropospheric ozone) is regarded as a pollutant by the World Health Organisation[11]. It is not emitted directly by car engines or by industrial operations. It is formed by the reaction of sunlight on air containing hydrocarbons and nitrogen oxides that to form ozone directly at the source of the pollution or many kilometers down wind. For more details of the complex chemical reactions that produce low level ozone see tropospheric ozone or Seinfled and Pandis (1998).

Ozone reacts directly with some hydrocarbons such as aldehydes and thus begins their removal from the air, but the products are themselves key components of smog. Ozone photolysis by UV light leads to production of the hydroxyl radical and this plays a part in the removal of hydrocarbons from the air, but is also the first step in the creation of components of smog such as peroxyacyl nitrates which can be powerful eye irritants. The atmospheric lifetime of tropospheric ozone is about 22 days and its main removal mechanisms are being deposited to the ground, the above mentioned reaction giving OH, and by reactions with OH and the peroxy radical $HO_2\cdot$ (Stevenson et al, 2006) [12].

As well as having impact on human health (see below) there is also evidence of significant reduction in agricultural yields due to increased ground-level ozone and pollution which interferes with photosynthesis and stunts overall growth of some plant species.[13][14]

Ozone as a greenhouse gas

Although ozone was present at ground level before the industrial revolution, peak concentrations are far higher than the pre-industrial levels and even background concentrations well away from sources of pollution are substantially higher.[15][16] This increase in ozone is of further concern as ozone present in the upper troposphere acts as a greenhouse gas, absorbing some of the infrared energy emitted by the earth. Quantifying the greenhouse gas potency of ozone is difficult as it is not present in uniform concentrations across the globe. However, the most recent scientific review on the climate change (the IPCC Third Assessment Report[17]) suggests that the radiative forcing of tropospheric ozone is about 25% that of carbon dioxide.

Ozone and health

Ozone in air pollution

There is a great deal of evidence to show that high concentrations (ppm) of ozone, created by high concentrations of pollution and daylight UV rays at the earth's surface, can harm lung function and irritate the respiratory system [11][18]. There has also been shown to be a connection between increased ozone caused by thunderstorms and hospital admissions of asthma sufferers [19]. Air quality guidelines such as those from the World Health Organization are based on detailed studies of what levels can cause measurable health effects.

Physiology of ozone

Ozone, along with reactive forms of oxygen such as superoxide, singlet oxygen (see oxygen), hydrogen peroxide, and hypochlorite ions, is naturally produced by white blood cells and other biological systems (such as the roots of marigolds) as a means of destroying foreign bodies. Ozone reacts directly with organic double bonds. Also, when ozone breaks down to dioxygen it gives rise to oxygen free radicals, which are highly reactive and capable of damaging many organic molecules. Ozone has been found to convert cholesterol in the blood stream to plaque (which causes hardening and narrowing of arteries). Moreover, it is believed that the powerful oxidizing properties of ozone may be a contributing factor of inflammation. The cause-and-effect relationship of how the ozone is created in the body and what it does is still under consideration and still subject to various interpretations, since other body chemical processes can trigger some of the same reactions. A team headed by Dr. Paul Wentworth Jr. of the Department of Chemistry at the Scripps Research Institute has shown evidence linking the antibody-catalyzed water-oxidation pathway of the human immune response to the production of ozone. In this system, ozone is produced by antibody-catalyzed production of trioxidane from water and neutrophil-produced singlet oxygen. [20]. See also trioxidane for more on this biological ozone-producing reaction.

Ozone has also been proven to form specific, cholesterol-derived metabolites that are thought to facilitate the build-up and pathogenesis of atherosclerotic plaques (A form of heart disease). These metabolites have been confirmed as naturally occurring in human atherosclerotic arteries and are categorized into a class of secosterols termed “Atheronals”, generated by ozonolysis of cholesterol's double bond to form a 5,6 secosterol as well as a secondary condensation product via aldolization.[21] Volume: Number: Page: 23 DOI:

Safety

Artificial production

Ozone may be formed from O_2 by electrical discharges and by action of high energy electromagnetic radiation. Certain electrical equipment generate significant levels of ozone. This is especially true of devices using high voltages, such as laser printers, photocopiers, and arc welders. Electric motors using brushes can generate ozone from repeated sparking inside the unit. Large motors, such as those used by elevators or hydraulic pumps, will generate more ozone than smaller motors.

Industrial production

Ozone used in industry is measured in ppm or mg/L (OSHA exposure limits for example), and percent by mass or weight. Industrially, ozone is produced with short wavelength ultraviolet radiation from a mercury vapor lamp or the application of a high voltage electrical field in a process called cold or corona discharge. The cold discharge apparatus consists of two metal plates separated by an air gap and a high dielectric strength electrical insulator such as borosilicate glass or mica. A high voltage alternating current is applied to the plates and the ozone is formed in the air gap when O2 molecules disassociate and recombine into O3. A faint corona may be present in the air gap, but the voltage is maintained below that

which would cause punch-through of the insulator with subsequent arcing and plasma formation.

Laboratory production

In the laboratory ozone can be produced by electrolysis using a 9 volt battery, a pencil graphite rod cathode, a platinum wire anode and a 3M sulfuric acid electrolyte.[22] The half cell reactions taking place are:

3 H_2O ’ O_3 + 6 H^+ + 6 e ”E^o = 1.53 V 6 H^+ + 6 e ’ 3 H_2 ”E^o = 0 V 2 H_2O ’ O_2 + 4 H^+ + 4 e ”E^o = 1. 23 V

So that in the net reaction three equivalents of water are converted into one equivalent of ozone and three equivalents of hydrogen. Oxygen formation is a competing reaction.

Applications

Industrial applications

Ozone can be used for bleaching substances and for killing bacteria. Many municipal drinking water systems kill bacteria with ozone instead of the more common chlorine. Ozone does not form organochlorine compounds, but it also does not remain in the water after treatment, so some systems introduce a small amount of chlorine to prevent bacterial growth in the pipes, or may use chlorine intermittently, based on results of periodic testing. Where electrical power is abundant, ozone is a cost-effective method of treating water, as it is produced on demand and does not require transportation and storage of hazardous chemicals. Once it has decayed, it leaves no taste or odor in drinking water. Low level of Ozone is helpful to purify air inside the house. Eliminate mildew and mold build up.

Industrially, ozone or ozonated water is used to

- disinfect water before it is bottled;
- deodorize air and objects, such as after a fire;
- kill bacteria on food or on contact surfaces;
- scrub yeast and mold spores from the air in food processing plants;
- wash fresh fruits and vegetables to kill yeast, mold and bacteria;
- chemically attack contaminants in water (iron, arsenic, hydrogen sulfide, nitrites, and complex organics lumped together as "color");
- provide an aid to flocculation (agglomeration of molecules, which aids in filtration, where the iron and arsenic are removed);
- clean and bleach fabrics (the latter use is patented);
- assist in processing plastics to allow adhesion of inks;
- age rubber samples to determine the useful life of a batch of rubber;
- in surface water treatment plants to eradicate water borne parasites such as Giardia and Cryptosporidium. This process is known as ozonation.

Ozone is a reagent in many organic reactions in the laboratory and in industry. Ozonolysis is the cleavage of an alkene to carbonyl compounds.

Many hospitals in the U.S. and around the world use large ozone generators to decontaminate operating rooms between surgeries. The rooms are cleaned and then sealed airtight before being filled with ozone which effectively kills or neutralizes all remaining bacteria.

Consumer applications

Ozone machines, with or without ionization, are currently used to sanitize (high ozone output) and deodorize non-inhabited rooms, ductwork, vehicles, boats, woodsheds, and buildings.

Some models of air purifiers that also emit low levels of ozone have been sold in the US. These type of air purifiers claim to imitate nature's "filterless" air purifying mechanisms [23] and claim to "sanitize" the air and/or household surfaces. The government successfully sued one company in 1995, ordering them to stop repeating health claims without supporting scientific studies.

Ozonated water is used to launder clothes, sanitize food, drinking water, and surfaces in the home. According to the FDA, it is "amending the food additive regulations to provide for the safe use of ozone in gaseous and aqueous phases as an antimicrobial agent on food, including meat and poultry." Ironically, while ozone is considered an atmospheric pollutant, pollution and smog by the US government, it can actually reduce pollutants like pesticides in fruits and vegetables.[24]

Ozone is used in spas or hot tubs with reduced levels of Chlorine or Bromine for keeping the water free of bacteria. As it does not remain in the water after treatment, it is ineffective at preventing bather cross-contamination, and must be used in conjuction with another sanitizer. Ozone gas is created by an ultraviolet light bulb or corona discharge chip and injected into the plumbing system.

Ozone is also widely used in treatment of water in aquaria and fish ponds. Its use can minimise bacterial growth control parasites and removes or reduce "yellowing" of the water. As the Ozone rapidly decomposes, at correctly controlled levels the application has no effect on the fish.

Pharmaceutical applications

Ozone has a number of medical uses. It can be used to affect the body's antioxidant-prooxidant balance, since the body usually reacts to its presence by producing antioxidant enzymes.[citation needed] Ozone therapy has blossomed into a thriving field of alternative medicine, with a host of claimed applications far above and beyond what has actually been verified by studies .

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Potassium permanganate

Other names Potassium manganate(VII)

Molecular formula $KMnO_4$

Molar mass 158.04 g/mol

Appearance black needles; vivid purple in solution

CAS number [7722-64-7]

Properties

Density and phase 2.703 g/cm**3**, solid

Solubility in water 6.38 g/100 ml (20 °C)

Melting point 270 °C decomp.

Thermodynamic data

Standard enthalpy of formation ”***f***H°***solid*** 813.4 kJ/mol

Standard molar entropy S°***solid*** 171.7 J.K**1**.mol**1**

Hazards

EU classification

Oxidant (*O*)
Harmful (*Xn*)
Dangerous for
the environment (*N*)
R-phrases R8, R22, R50/53

S-phrases S2, S60, S61

Related compounds

Other anions Potassium perrhenate

Other cations Sodium permanganate

Related compounds Potassium manganite, Potassium manganate, Manganese heptoxide

Except where noted otherwise, data are given for materials in their standard state (at 25 °C, 100 kPa)

Potassium permanganate is the chemical compound KMnO4. In this salt, manganese is in the +7 oxidation state. The salt is also known as "permanganate of potash" and "Condy's crystals". The permanganate ion is a strong oxidizing agent. It dissolves in water to give deep purple solutions, evaporation of which gives prismatic purple-black glistening crystals.[1] It has a sweet taste and is odourless.

History

In 1659 a German chemist, J.R. Glauber, fused a mixture of the mineral pyrolusite and potassium carbonate to obtain a material that, when dissolved in water, gave a green solution (sodium manganate) which slowly changed colour to violet (*potassium permanganate*) and then finally red. This report represents the first description of the production of potassium permanganate.

Just under 200 years later a Londoner named Henry Bollmann Condy trained as a chemist. He had an interest in disinfectants and marketed a number of products including ozonised water. He found that when he fused pyrolusite with NaOH and dissolved the product in water it gave a solution that had good disinfectant properties. He patented this solution, and marketed it as Condy's Fluid. The problem was that the solution, although quite effective, was not very stable. This difficulty was overcome by using KOH rather than NaOH. This gave a more stable material, which had the added advantage of being easily converted to the equally effective potassium permanganate crystals. This crystalline material was known as Condy's crystals or Condy's powder. Potassium permanganate was comparatively easy to manufacture so Condy was subsequently forced to spend considerable time in litigation in order to stop competitors from marketing products similar to Condy's Fluid or Condy's Crystals.

Early photographers used it as a component of flash powder.

Uses

Chemical applications

Potassium permanganate is used as an oxidizing agent in diverse chemical reactions in the laboratory and in industry.[3] It also serves as a disinfectant and in deodorizers. It can be used as a reagent for the synthesis of many different kinds of chemical compounds. In wastewater treatment, it is used to neutralize hydrogen sulfide. In analytical chemistry, a standardized aqueous solution of $KMnO_4$ is sometimes used as an oxidizing titrant for redox titrations due to its deep purple color. In a related way, it is used as a reagent to determine the Kappa number of wood pulp. Mixing potassium permanganate and formaldehyde forms a mild tear gas.

As an oxidant in organic synthesis

Dilute solutions of $KMnO_4$ convert alkenes into diols (glycols). This behaviour is also used as a qualitative test for the presence of double or triple bonds in a molecule, since the reaction decolorizes the permanganate solution; thus it is sometimes referred to as Baeyer's reagent.

Concentrated solutions oxidize a methyl group on an aromatic ring, e.g. toluene to benzoic acid.

$KMnO_4$ oxidizes pseudoephedrine hydrochloride to produce methcathinone, a Schedule I drug in the United States. Consequently the DEA has restricted its use and sale by classifying it as a List I controlled precursor. Potassium permanganate is listed as a Table I precursor

under the United Nations Convention Against Illicit Traffic in Narcotic Drugs and Psychotropic Substances.[1]

Acids and KMnO4

diluted sulfuric acid reacts with KMnO4 to give Mn2O7, which can be explosive.[4][5][6]. Similarly concentrated HCl gives chlorine. The Mn-containing products from redox reactions depend on the pH. Acidic solutions of permanganate are reduced to the faintly pink [Mn(H2O)6]2+. In neutral solution, permanganate is only reduced by 5e- to give a soluton of Mn2+ (aq), wherein Mn is in a +2 oxidation state. This is the material that stains one's skin when handling KMnO4. KMnO4 spontaneously reduced in an alkaline solution to green-coloured K2MnO4, wherein manganese is in the +6 oxidation state.

A curious reaction is observed when one adds concentrated sulfuric acid to potassium permanganate. Although no reaction may be apparent, the vapor over the mixture will ignite paper impregnated with alcohol. Potassium permanganate and sulfuric acid react to produce some ozone, which has a high oxidising power and rapidly oxidises the alcohol, causing it to combust. An approximate equation for the ozone formation is shown below.

At room temperature 6 $KMnO_4(aq) + 9\ H_2SO_4(aq)$ ’ 6 $MnSO_4(aq) + 3\ K_2SO_4(aq) + 9\ H_2O(l) + 5\ O_3(g)$

Biomedical uses

- Dilute solutions are used as a treatment for canker sores (ulcers) (0.25%), disinfectant for the hands (about 1%) and treatment for mild pompholyx dermatitis or fungal infections of the hands or feet.
- A dilute solution of acidified potassium permanganate is used in histology to bleach melanin which obscures tissue detail.
- Potassium permanganate can be used to differentiate amyloid AA from other types of amyloid pathologically deposited in body tissues. Incubation of fixed tissue with potassium permanganate will prevent amyloid AA from staining with congo red whereas other types of amyloid are unaffected.[7][8]

Miscellaneous uses

- Aqueous solutions of $KMnO_4$ have been used together with T-Stoff (i.e. 80 % hydrogen peroxide) as propellant for the rocket plane Messerschmitt Me 163. In this application, it was known as Z-Stoff. This combination of propellants is still used in torpedoes.
- A dilute (10mg/l) of potassium permanganate can be used to eliminate snails from plants prior to placing them in a fresh-water aquarium.
- High-grade potassium permanganate can be found at pool supply stores and is used in rural areas to remove iron and hydrogen sulfide (rotten egg smell) from well water.

- $KMnO_4$ is often included in survival kits along with either glycerine or a glucose tablet for the purposes of making fire. The glucose tablet can be ground up, mixed with the potassium permanganate and caused to combust by applying friction. It can also be mixed with anti-freeze from a vehicle to produce flame, although this can be dangerous and should be done in a controlled manner ie dipping some paper into the anti-freeze and then adding a small amount of potassium permanganate. The ability to sterilise water and wounds is also advantageous and another reason for inclusion in a survival kit.
- $KMnO_4$ is employed to treat some parasitic diseases of fish, in treatment of drinking water, as well as an antidote in phosphorus poisoning. In Africa, it has been used as a disinfectant for vegetables such as lettuce.

Hazards

Solid $KMnO_4$ is a strong oxidizer and in general it should be kept separated from oxidisible substances. For more information consult an MSDS. Some reactions need a bit of a solvent, for example, powdered potassium permanganate + powdered sugar will ignite (but not explode) a few seconds after a drop of water is added. Dilute aqueous solutions of $KMnO_4$ are not dangerous. $KMnO_4$ forms dangerous products upon contact with concentrated acids.

Potassium permanganate stains the hand and clothing (as it is reduced to MnO_2) and should be handled with care. Clothing stains may be washed away using acetic acid. Skin stains disappear within 48 hours.

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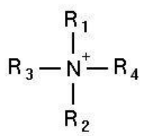
1. ^ Red list

Quaternary ammonium cation



Quaternary ammonium cation. Any or all of the R groups may be the same or different alkyl groups. Also, any of the R groups may be connected.

Quaternary ammonium cations, also known as *quats*, are positively charged polyatomic ions of the structure NR4+ with R being alkyl groups. Unlike the ammonium ion NH4+ itself and primary, secondary, or tertiary ammonium cations, the quaternary ammonium cations are permanently charged, independent of the pH of their solution. Quaternary ammonium cations are synthesized by complete alkylation of ammonia or other amines.

Quaternary ammonium salts or *quaternary ammonium compounds* are salts of quaternary ammonium cations with an anion. They are used as disinfectants, surfactants, fabric softeners, antistatic agents (e.g. in shampoo), and phase transfer catalysts. In liquid fabric softeners, the chloride salts are often used. In dryer anticling strips, the sulfate salts are often used.

The synthesis of this cation from ammonia is referred to as *quaternization*.

See also

- Benzalkonium chloride, a common quaternary disinfectant
- Denatonium, the bitterest compound known
- Cocamidopropyl betaine, a common surfactant
- Cetyl trimethylammonium bromide (CTAB), one of the most investigated cationic surfactant compounds
- Aliquat 336, a phase transfer catalyst

Preservatives

A *preservative* is a natural or synthetic chemical that is added to products such as foods, pharmaceuticals, paints, biological samples, etc. to retard spoilage, whether from microbial growth, or undesirable chemical changes.

Preservatives may be added to wood to prevent the growth of fungi as well as to repel insects and termites. Typically copper, borate, and petroleum based chemical compounds are used. For more information on wood preservatives see timber treatment, lumber and creosote.

Preservative food additives are often used alone, or in conjunction with other methods of food preservation. A distinction is sometimes made between anti-microbial preservatives which function by inhibiting the growth of insects, bacteria and fungi, and antioxidants such as Oxygen absorbers, which inhibit the oxidation of food constituents. Common anti-microbial preservatives include sodium nitrate, sodium nitrite, sulfites (sulfur dioxide,

sodium bisulfite, potassium hydrogen sulfite, etc.) and disodium EDTA. Antioxidants include BHA and BHT. Other preservatives include formaldehyde (usually in solution), glutaraldehyde, diatomaceous earth (kills insects), ethanol, dimethyl dicarbonate and methylchloroisothiazolinone. The benefits and safety of many artificial food additives (including preservatives) are the subject of debate among academics specializing in food science and toxicology.

Some methods of food preservation involve the use of salt, sugar or vinegar, which are sometimes considered to be foods rather than additives. Some people believe preservatives are harmful to human health.

Edible salt

Edible salt, also called *table salt* or just *salt*, is a mineral, one of a very few rocks commonly eaten by humans. There are different forms of edible salt: unrefined salt, refined salt, table salt or iodised salt. It is a crystalline solid, white, pale pink or light grey in colour, obtained from sea water or from rock deposits. Sea salt comes in fine or larger crystals. In nature, it includes not only sodium chloride, but also other vital trace minerals. Edible rock salts may be slightly greyish in colour due to this mineral content.

Salt is necessary for the survival of all living creatures, including humans. Salt is involved in regulating the water content (fluid balance) of the body. Salt flavour is one of the basic tastes. Salt cravings may be caused by trace mineral deficiencies as well as by a deficiency of sodium chloride itself.

Salt is required for life, but overconsumption can increase the risk of health problems, including high blood pressure, in those individuals who are genetically predisposed to hypertension. In food preparation, salt is used as a preservative and as a seasoning.

History of edible salt

Salt's preservative ability was a foundation of civilization. It eliminated dependency on the seasonal availability of food, allowed travel over long distances, and was a vital food additive. However, because salt(NaCl) was difficult to obtain, it became a highly valued trade item throughout history. Until the 1900s, salt was one of the prime movers of national economies and wars. Salt was often taxed; research has discovered this practice to have existed as early as the 20th century BC in China.

In the empire of Mali, merchants in 12th century Timbuktu—the gateway to the Sahara Desert and the seat of scholars—valued salt (NaCl) enough to buy it for its weight in gold; this trade led to the legends of the incredibly wealthy city of Timbuktu, and fueled inflation in Europe, which was exporting the salt.

Forms of edible salt

Unrefined salt

Different natural salts have different mineralities, giving each one a unique flavor. Fleur de sel, natural sea salt harvested by hand, has a unique flavor varying from region to region.

Some assert that unrefined sea salt is more healthy than refined salts. There are concerns, however, that raw sea or rock salts may not contain sufficient iodine salts to prevent iodine deficiency diseases like goitre.

Refined salt

Refined salt, that is most widely used presently, is mainly sodium chloride. Only about 7% of refined salt is used as a food additive. The majority is sold for industrial use, from manufacturing pulp and paper to setting dyes in textiles and fabric, to producing soaps and detergents, and has great commercial value.

The manufacture and use of salt is one of the oldest chemical industries. Salt is also obtained by evaporation of sea water, usually in shallow basins warmed by sunlight; salt so obtained was formerly called bay salt, and is now often called sea salt or solar salt. Today, most refined salt is prepared from rock salt: mineral deposits high in edible salt. These rock salt deposits were formed by the evaporation of ancient salt lakes. These deposits may be mined conventionally or through the injection of water. Injected water dissolves the salt, and the brine solution can be pumped to the surface where the salt is collected.

After the raw salt is obtained, it is refined to purify it and improve its storage and handling characteristics. Purification usually involves recrystallization. In recrystallization, a brine solution is treated with chemicals that precipitate most impurities (largely magnesium and calcium salts). Multiple stages of evaporation are then used to collect pure sodium chloride crystals, which are kiln-dried.

Anticaking agents (and potassium iodide, for iodised salt) are generally added at this point. These agents are hygroscopic chemicals which absorb humidity, keeping the salt crystals from sticking together. Some anticaking agents used are tricalcium phosphate, calcium or magnesium carbonates, fatty acid salts (acid salts), magnesium oxide, silicon dioxide, sodium alumino-silicate, and alumino-calcium silicate. Concerns have been raised regarding the possible toxic effects of aluminium in the latter two compounds, however both the European Union and the United States Food and Drug Administration (FDA) permit their use in regulated quantities. The refined salt is then ready for packing and distribution.

Table salt

Table salt is refined salt, nearly pure (95% or greater) sodium chloride. It usually contains substances that make it free flowing (anticaking agents) such as sodium silicoaluminate as well as a minute amount of invert sugar to prevent the salt from turning a yellow colour when exposed to sunlight, and to prevent a significant loss of iodine via vaporization. It is common practice to put a few grains of uncooked rice in salt shakers to

absorb extra moisture when anticaking agents are not enough. Table salt is also often iodised—a small amount of potassium iodide is added as an important dietary supplement. Table salt is mainly employed in cooking and as a table condiment. Iodised table salt has significantly reduced disorders of iodine deficiency in countries where it is used. Iodine is important to prevent the insufficient production of thyroid hormones (hypothyroidism), which can cause goitre, cretinism in children, and myxedema in adults.

Table salt is now used all over the world.

Health effects

Sodium is one of the primary electrolytes in the body. All three electrolytes (sodium, potassium, and calcium) are available in unrefined salt, as are other vital minerals needed for optimal bodily function. Too much or too little salt in the diet can lead to muscle cramps, dizziness, or even an electrolyte disturbance, which can cause severe, even fatal, neurological problems. Drinking too much water, with insufficient salt intake, puts a person at risk of water intoxication. Salt is even sometimes used as a health aid, such as in treatment of dysautonomia. Some sources claim that salt is actually good for you, especially South Korean salt[2]

People's risk for disease due to salt intake that is too low or too high varies, due to biochemical individuality. In fact, some have asserted that while the risks of consuming too much salt are real, the risks have been dramatically overhyped for most people, or that the studies done on the consumption of edible salt can be interpeted in many different ways.[3][4]

Nevertheless, salt has been studied extensively by researchers and many of them believe that salt can be consumed in excess and can therefore lead to health problems.

For example, salt consumption has been linked to exercise-induced asthma.[5] On the other hand, another source counters, "...we still don't know whether salt contributes to asthma. If there is a link then it's very weak...".[6] Excessive salt intake may also trigger heartburn[7]. The role of salt in the causation or exacerbation of osteoporosis is similarly plausible. One report shows that a high salt diet does reduce bone density in girls.[8]. Yet "While high salt intakes have been associated with detrimental effects on bone health, there are insufficient data to draw firm conclusions." ([9], p3) Gastric cancer (Stomach cancer) is associated with high levels of sodium, "but the evidence does not generally relate to foods typically consumed in the UK." ([9], p18)

Studies have clearly shown a link between an overabundance of salt in the diet and hypertension (high blood pressure). "Since 1994, the evidence of an association between dietary salt intakes and blood pressure has increased. The data have been consistent in various study populations and across the age range in adults." ([9] p3). "The CMO [Chief Medical Officer] of England, in his Annual Report (DH, 2001), highlighted that people with high blood pressure are three times more likely to develop heart disease and stroke, and twice as likely to die from these diseases than those with normal levels."([9], p14). Professor Dr. Diederick Grobbee claims that there is no evidence of a causal link between salt intake and mortality or cardiovascular events.[10]. One study found that low urinary sodium is associated with greater risk of myocardial infarction among treated hypertensive men [11]. Additionally, in a study of left ventricular hypertrophy (cardiac enlargement), "Evidence

suggests that high salt intake causes left ventricular hypertrophy, a strong risk factor for cardiovascular disease, independently of blood pressure effects." ([9] p3) "...there is accumulating evidence that high salt intake predicts left ventricular hypertrophy." ([12], p12) Excessive salt (sodium) intake, combined with an inadequate intake of water, can cause hypernatremia. It can exacerbate renal disease.[1]

A decrease in salt intake has been suggested to treat many health conditions as well, such as edema (BE: oedema) (fluid retention).[13][1]

Recommended intake

This section summarizes the salt intake recommended by the health agencies of various countries. Recommendations tend to be similar. Note that targets for the population as a whole tend to be pragmatic (what is achievable) while advice for an individual is ideal (what is best for health). For example, in the UK target for the population is "eat no more than 6g a day" but for a person is 4g.

Intakes can be expressed variously as salt or sodium and in various units.

- 1g sodium = 1,000mg sodium = 42 mmol sodium = 2.5g salt

United Kingdom: In 2003, the UK's Scientific Advisory Committee on Nutrition (SACN) recommended that, for a typical adult, the Reference Nutrient Intake (the amount you need) is 4g salt per day (1.6g or 70 mmol sodium). However, average adult intake is two and a half times the Reference Nutrient Intake for sodium. "Although accurate data are not available for children, conservative estimates indicate that, on a body weight basis, the average salt intake of children is higher than that of adults." SACN aimed for an achievable target reduction in average intake of salt to 6g per day (2.4g or 100 mmol sodium) — this is roughly equivalent to a teaspoonful of salt. The SACN recommendations for children are:

- 0–6 months old: less than 1g/day
- 7–12 months: 1g/day
- 1–3 years: 2g/day
- 4–6 years: 3g/day
- 7–10 years: 5g/day
- 11–14 years: 6g/day

SACN states, "The target salt intakes set for adults and children do not represent ideal or optimum consumption levels, but achievable population goals."[9]

Republic of Ireland: The Food Safety Authority of Ireland endorses the UK targets "emphasising that the RDA of 1.6g sodium (4g salt) per day should form the basis of advice targeted at individuals as distinct from the population health target of a mean salt intake of 6g per day."([12], p16)

Canada: Health Canada recommends an Adequate Intake (AI) and an Upper Limit (UL) in terms of *sodium*.

- 0–6 months old: 0.12g/day (AI)
- 7–12 months: 0.37g/day (AI)
- 1–3 years: 1g/day (AI) 1.5g/day (UL)
- 4–8 years: 1.2/day (AI) 1.9g/day (UL)
- 9–13 years: 1.5g/day (AI) 2.2g/day (UL)

- 14–50 years: 1.5g/day (AI) 2.3g/day (UL)
- 51–70 years: 1.3g/day (AI) 2.3g/day (UL)
- 70 years and older: 1.2g/day (AI) 2.3g/day (UL)[14]

New Zealand

- Adequate Intake (AI) 0.46 – 0.92g sodium = 1.2 – 2.3g salt
- Upper Limit (UL)) 2.3g sodium = 5.8g salt[15]

Australia: The recommended dietary intake (RDI) is 0.92g–2.3g sodium per day (= 2.3g–5.8g salt)[16]

USA: The Food and Drug Administration itself does not make a recommendation[17] but refers readers to Dietary Guidelines for Americans 2005. These suggest that US citizens should consume less than 2,300 mg of sodium (= 2.3g sodium = 5.8g salt) per day. [18]

Labeling

The FDA Food Labeling Guide stipulates whether a food can be labelled as "free", "low", or "reduced/less" in respect of sodium. A food that exceeds 480mg of sodium per 'serving' must have a disclosure statement.[19]

Campaigns

In 2004, the Food Standards Agency started a public health campaign called "Salt - Watch it", which recommends no more than 6g of salt per day; it features a character called Sid the Slug and was criticised by the Salt Manufacturers Association (SMA).[20] The Advertising Standards Authority did not uphold the SMA complaint in its adjudication.[21].

Salt substitutes

Salt intake can be reduced quite easily by simply reducing salty foods in one's diet. Salt substitutes have a taste similar to table salt and contain mostly potassium chloride, which will increase potassium intake. Because excess potassium intake can cause potentially fatal hyperkalemia, it is advisable to check with one's physician and pharmacist before using salt substitutes. Various diseases and medications may decrease the body's excretion of potassium, thereby increasing the risk of hyperkalemia. If you have kidney failure, heart failure or have diabetes, you should not use a low salt variety without medical advice. A manufacturer, LoSalt, has issued an advisory statement.[22] that people taking the following prescription drugs should not use a salt substitute: Amiloride, Triamterene, Dytac, Spironolactone, Aldactone, Eplerenone, and Inspra.

See also

- Sodium chloride

References

1. ^ a ***b*** ***c*** Australia: Better Health Channel (Australia, Victoria) Salt

2. ^ Cleveland Clinic Health Information Center Dysautonomia page

3. ^ **Why Files article** Salt and other wounds

4. ^ Gary Taubes, "The (Political) Science of Salt", Science, 14 August 1998, Vol. 281. no. 5379, pp. 898 - 907

5. ^ Exercise-induced asthma more clearly linked to high-salt diet

6. ^ **Dr Trisha Macnair** "Does eating salt make asthma worse?"

7. ^ **Everybody** Study adds salt to suspected triggers for heartburn

8. ^ High salt diet reduces bone density in girls

9. ^ a ***b*** c d e ***f*** Scientific Advisory Committee on Nutrition (SACN) Salt and Health (PDF)

10. ^ Salt Manufacturers' Association press release

11. ^ **Michael H. Alderman; Shantha Madhavan; Hillel Cohen; Jean E. Sealey; John H. Laragh** Low Urinary Sodium Is Associated With Greater Risk of Myocardial Infarction Among Treated Hypertensive Men *Hypertension* **1995;25:1144-1152.**

12. **^** a b **Food Safety Authority of Ireland** Salt and Health: Review of the Scientific Evidence and Recommendations for Public Policy in Ireland

13. ^ Australia: Better Health Channel (Australia, Victoria) Fluid retention
14. ^ Health Canada Dietary Reference Intakes (look for Sodium)
15. ^ Auckland District Health Board Public Health Nutrition Advice (PDF)
16. ^ Better Health Channel (Australia, Victoria) Salt

17. ^ **U. S. Food and Drug Administration** A Pinch of Controversy Shakes Up Dietary Salt

18. ^ Department of Health and Human Services (HHS) and the Department of Agriculture (USDA) Dietary Guidelines for Americans 2005 "Sodium and Potassium"

19. ^ **Food and Drug Administration** A Food Labeling Guide--Appendix A

20. ^ Salt Manufacturers Association press release New salt campaign under attack

21. ^ **Advertising Standards Authority** Broadcast Advertising Adjudications: 20 April 2005 **(PDF)**

22. ^ **LoSalt** Advisory Statement **(PDF)**

Further reading

- Mark Kurlansky, Salt : A World History, Penguin Books
- Department of Health, Dietary Reference Values for Food Energy and Nutrients for the UK: Report of the Panel on DRVs of the Committee on the Medical Aspects of Food Policy , The Stationery Office

Potassium nitrate

Other names Saltpetre, Nitrate of potash

Molecular formula KNO_3

Molar mass 101.1032 g/mol

Appearance white solid

CAS number [7757-79-1]

Properties

Density and phase 2.1 g/cm^3, solid

Solubility in water 35.7 g/100 ml (25 °C)

Melting point 334 °C

Boiling point 400 °C decomp.

Structure

Crystal structure Orthorhombic, Aragonite

Hazards

MSDS External MSDS

Related compounds

Other anions Potassium nitrite

Other cations Lithium nitrate, Sodium nitrate, Rubidium nitrate, Caesium nitrate

Except where noted otherwise, data are given for materials in their standard state (at 25 °C, 100 kPa)

The chemical compound *potassium nitrate* is a naturally occurring mineral source of nitrogen. It is a nitrate with chemical formula KNO3.

Its common names include *saltpetre* (from Medieval Latin *sal petrae*: "stone salt" or possibly "Salt of Petra"), American English *salt peter*, *Nitrate of potash* and *nitre*. The name salt peter is also applied to sodium nitrate.

Description

Potassium nitrate is the oxidizing (oxygen-supplying) component of black powder. Prior to the large-scale industrial fixation of nitrogen through the Haber process, a major source of Potassium nitrate was the deposits crystallising from cave walls or the drainings of decomposing organic material. Dung-heaps were a particularly common source: ammonia from the decomposition of urea and other nitrogenous materials would undergo bacterial oxidation to produce nitrate. It was and is also used as a component in some fertilizers. When used by itself as a fertilizer, it has an NPK rating of 13-0-44 (indicating 13%, 0%, and 44% of nitrogen, phosphorus, and potassium, by mass, respectively). Potasium nitrate is also used to fuse with sugar to make common smoke bombs.

Manufacture

Historically, nitre-beds were prepared by mixing manure with either mortar or wood ashes, common earth and organic materials such as straw to give porosity to a compost pile typically 1.5 metres high by 2 metres wide by 5 metres long. The heap was usually under a cover from the rain, kept moist with urine, turned often to accelerate the decomposition and leached with water after approximately one year. The liquid containing various nitrates was then converted with wood ashes to potassium nitrates, crystallized and refined for use in gunpowder. Today, most potassium nitrate comes from the vast deposits of sodium nitrate (NaNO3, nitratine) in the Chilean deserts. The sodium nitrate is purified and then reacted in solution with potassium chloride (KCl, sylvite), from which the less-soluble potassium nitrate is precipitated out.

In England, the privilege of manufacturing explosives had been in the hands of the family of John Evelyn, the celebrated diarist, as a crown monopoly since before 1588.

Applications

One of the most useful applications of potassium nitrate is in the production of nitric acid, by adding concentrated sulfuric acid to an aqueous solution of potassium nitrate, yielding nitric acid and potassium sulfate which are separated through fractional distillation.

Potassium nitrate is also used as a fertilizer, in model rocket propellant, and in several fireworks such as smoke bombs, in which a mixture with sugar produces a smoke cloud of 600 times their own volume. The ratio for smoke bombs using sucrose (powdered sugar) and potassium nitrate is 40($C_{12}H_{22}O_{11}$):60(KNO_3). It can be used as is, or carefully melted together using a hot plate.

In the process of food preservation, potassium nitrate is a rare ingredient of salted meat, but there are theories indicating that using nitrates in meats can cause cancer. As a preservative it can be known as E252.

Potassium Nitrate is also a main component in stump remover; it accelerates the natural decomposition of the stump. Stump remover is usually about 98% pure KNO_3, and is a common source of KNO_3.

It has also been used in the manufacture of ice cream and can be found in some toothpastes for sensitive teeth. Recently, the use of potassium nitrate in toothpastes for sensitive teeth has increased dramatically, despite the fact that it has not been conclusively shown to help dental hypersensitivity.

A popular misconception is that potassium nitrate is an anaphrodisiac and was added to food in all-male institutions. In fact, potassium nitrate has no such effect in humans. [2]

Although potassium nitrate is used in gunpowder, by itself, potassium nitrate is not combustible or flammable.

References in Literature

- Potassium Nitrate is used in Edgar Allen Poe's famous short story "The Cask of Amontillado" as nitre which lines the crypt where Monstresor buries Fortunato alive.
- The "Book of Secrets" attributed to Albertus Magnus refers to this substance as "Stony Salt" ("salis petrosi" in Latin).

See also

- Sodium nitrate
-

Sodium nitrate

Name Sodium nitrate

Chemical formula $NaNO_3$

Appearance White powder or colorless crystals

CAS number [7631-99-4]

Physical

Formula weight 84.9947 amu

Melting point 580 K (307 °C)

Boiling point decomposes at 653 K (380 °C)

Density 2.3 ×103 kg/m3

Crystal structure Trigonal

Solubility 92 g in 100mL water

Critical relative humidity 72.4% (30 °C)

Thermochemistry

”***f***H**0*****liquid*** -452 kJ/mol

”***f***H**0*****solid*** -468 kJ/mol

S**0*****solid*** 117 J/mol·K

Safety

Ingestion May cause gastroenteritis and abdominal pains.

Inhalation respiratory irritation

Skin May cause irritation.

Eyes May cause irritation.

More info MSDS

SI units were used where possible. Unless otherwise stated, standard conditions were used.

Sodium nitrate (not to be confused with sodium nitrite) is a type of salt ($NaNO_3$) which has long been used as an ingredient in explosives and in solid rocket propellants, as well as in glass and pottery enamel, and as a food preservative (such as in hot dogs), and has been mined extensively for those purposes. It is also variously known as *caliche*, *Chile saltpeter*, *saltpeter*, and *soda niter*.

The world's largest natural deposits of caliche ore were in the Atacama desert of Chile, and many deposits were mined for over a century, until the 1940s. The former Chilean saltpeter mining communities of Humberstone and Santa Laura were declared Unesco World Heritage sites in 2005.

Chile still has the largest reserves of caliche, with active mines in such locations as Pedro de Valdivia, Maria Elena and Pampa Blanca. Sodium nitrate, potassium nitrate, sodium sulfate and iodine are all obtained by the processing of caliche.

Sodium nitrate is also manufactured synthetically by reacting nitric acid with soda ash.

Applications

The compound has antimicrobial properties when used as a food preservative. It is found naturally in leafy green vegetables. It has possible health benefits for increasing oxygen to blood,[citation needed] as well as known health side effects in particular at high doses. Side effects may include increased risk of cancer (if intake occurs together with proteins, which builds cancerogenic nitrosamines), where according to MEDEM the US-NAS found no such evidence in experiments with laboratory animals. In case of overdosage the local poison control center is the contact of choice.

It can be used in the production of nitric acid by combining with sulfuric acid and subsequent separation through fractional distillation of the nitric acid, leaving behind a residue of sodium bisulfate.

Less common applications include an oxidizer used in gunpowder, in blackpowder rockets, and as replacement for potassium nitrate.

It can be used as a PCM.

Sulfur dioxide

Systematic name sulfur dioxide

Other names

Sulfur(IV) oxide
Sulfurous anhydride,
'sulphurous anhydride

Molecular formula SO_2

Molar mass 64.054 g mol1

Appearance colourless gas

CAS number [7446-09-5]

EINECS number 231-195-2

Properties

Density and phase 2.551 g/L, gas

Solubility in water 9.4 g/100 mL (25 °C)

Melting point 72.4 °C (200.75 K)

Boiling point 10 °C (263 K)

Critical Point 157.2°C at 7.87 MPa

Acidity (p*Ka*) 1.81

Structure

Molecular shape bent

Dipole moment 1.63 D

Thermodynamic data

Standard enthalpy of formation ”*f*H°***gas*** 296.84 kJ mol**1**

Standard molar entropy S°***gas*** 248.21 J K**1** mol**1**

Safety data

EU classification Toxic

R-phrases **R23**, **R34**

S-phrases S1/2, S9, S26 ,S36/37/39, S45

PEL-TWA (OSHA) 5 ppm (13 mg m**3**)

IDLH (NIOSH) 100 ppm

Flash point non-flammable

RTECS number WS4550000

Related compounds

Other cations

Selenium dioxide
Tellurium dioxide

Related compounds

Sulfur trioxide
Sulfuric acid

Except where noted otherwise, data are given for materials in their standard state (at 25 °C, 100 kPa)

Sulfur dioxide (also *sulphur dioxide*) is the chemical compound with the formula SO***2*. This important gas is the main product from the combustion of sulfur compounds and is of significant environmental concern. SO***2*** is often described as the "smell of burning sulfur."

SO***2*** is produced by volcanoes and in various industrial processes. Since coal and petroleum contain various amounts of sulfur compounds, their combustion generates sulfur dioxide. Further oxidation of SO2, usually in the presence of a catalyst such as NO2, forms H2SO4, and thus acid rain.

Preparation

Sulfur dioxide can be prepared by burning sulfur:

$S_8(s) + 8O_2(g)$ ’ $8SO_2(g)$

The combustion of hydrogen sulfide and organosulfur compounds proceeds similarly.

$2H_2S(g) + 3O_2(g)$ ’ $2H_2O(g) + 2SO_2(g)$

The roasting of sulfide ores such as iron pyrites and sphalerite (zinc blende) also gives SO_2:

$4FeS_2(s) + 11O_2(g)$ ’ $2Fe_2O_3(s) + 8SO_2(g)$ $2ZnS(s) + 3O_2(g)$ ’ $2ZnO(s) + 2SO_2(g)$

When anhydrous $CaSO_4$ is heated with coke and sand in the manufacture of cement, $CaSiO_3$, sulfur dioxide is a by-product.

$2CaSO_4(s) + 2SiO_2(s) + C(s)$ ’ $2CaSiO_3(s) + 2SO_2(g) + CO_2(g)$

Action of *hot concentrated sulphuric acid* on copper tunings will produce sulphur dioxide.

$Cu(s) + 2H_2SO_4(l)$ ’ $CuSO_4(s) + SO_2(g) + 2H_2O(l)$

Structure and bonding

SO_2 is a bent molecule with C_{2v} symmetry point group.

In terms of electron-counting formalisms, the sulfur atom has an oxidation state of +4, a formal charge of 0, and is surrounded by 5 electron pairs. From the perspective of molecular orbital theory, most of these electron pairs are non-bonding in character, as is typical for hypervalent molecules.

Uses

Sulfur dioxide is sometimes used as a preservative in alcoholic drinks, or dried apricots and other dried fruits due to its antimicrobial properties. The preservative is used to maintain the appearance of the fruit rather than prevent rotting. This can give fruit a distinctive chemical taste.

Sulfur dioxide is also a good reductant. In the presence of water, sulfur dioxide is able to decolorize substances that can be reduced by it; thus making it a useful reducing bleach for papers and delicate materials such as clothes.

This bleaching effect normally does not last very long. Oxygen in the atmosphere reoxidizes the reduced dyes, restoring the color. This might explain why older newspapers turn yellow, because paper used for newspaper is naturally yellow.

Sulfur dioxide is also used to make sulfuric acid, being converted to sulfur trioxide, and then to oleum, which is made into sulfuric acid. Sulfur dioxide for this purpose is made when sulfur combines with oxygen. This is called the contact process.

According to Claude Ribbe in The Crime of Napoleon, sulfur dioxide gas was used as an execution poison by the French emperor to suppress a slave revolt in Haiti early in the 19th century.

Prior to the development of Freons, sulfur dioxide was used as a refrigerant in home refrigerators.

H2SO3 is also called "hydrogen sulfite" or sulfurous acid.

Emissions

According to the US EPA (as presented by the 2002 World Almanac or in chart form [1]), the following amount of sulfur dioxide was released in the U.S. per year, measured in thousands of short tons:

**1999* 18,867

**1998* 19,491

**1997* 19,363

**1996* 18,859

**1990* 23,678

**1980* 25,905

**1970* 31,161

Due largely to the US EPA's Acid Rain Program, the U.S. has witnessed a 33 percent decrease in emissions between 1983 and 2002. This improvement resulted from flue gas desulfurization, a technology that enables SO2 to be chemically bound in power plants burning sulfur-containing coal or oil. In particular, calcium oxide reacts with sulfur dioxide to form calcium sulfite:

CaO + SO***2*** ' CaSO***3***

Aerobic oxidation converts this CaSO***3*** into CaSO***4***, gypsum. Most gypsum sold in Europe comes from flue gas desulfurization.

As of 2006, China is the world's largest sulfur dioxide polluter, with 2005 emissions estimated to be 25.49 million tons. This amount represents a 27% increase since 2000, and is roughly comparable with U.S. emissions in 1980.

Al-Mishraq, an Iraqi sulfur plant, was the site of a 2004 disaster resulting in the release of massive amounts of sulfur dioxide into the atmosphere.

Appendix: temperature dependence of aqueous solubility

22 g/100ml (0 °C) 15 g/100ml (10 °C) 11 g/100ml (20 °C) 9.4 g/100 ml (25 °C) 8 g/100ml (30 °C) 6.5 g/100ml (40 °C) 5 g/100ml (50 °C) 4 g/100ml (60 °C) 3.5 g/100ml (70 °C) 3.4 g/100ml (80 °C) 3.5 g/100ml (90 °C) 3.7 g/100ml (100 °C)

Antiobesity agents

Anti-obesity drugs include all pharmacological treatments intended to reduce or control weight. Because these drugs are intended to alter one of the fundamental processes of the human body, anti-obesity drugs are medically prescribed only in cases of morbid obesity, where weight loss is life-saving.

Mechanisms of action

Anti-obesity drugs operate through one or more of the following mechanisms:

- Suppression of the appetite.
- Increase of the body's metabolism.
- Interference with the body's ability to absorb specific nutrients in food.

For example, orlistat blocks fat breakdown and thereby prevents fat absorption.

Anorectics (also known as anorexigenics) are primarily intended to suppress the appetite, but most of the drugs in this class also act as stimulants (dexedrine, e.g.), and patients have abused drugs "off label" to suppress appetite (e.g. digoxin).

Side effects

Some anti-obesity drugs have severe and often life-threatening side effects. (See, for example, Fen-phen.) These side effects are often associated with their mechanism of action. In general, stimulants carry a risk of high blood pressure, faster heart rate, palpitations, closed-angle glaucoma, drug addiction, restlessness, agitation, and insomnia.

Another drug, Orlistat, blocks absorption of dietary fats, and as a result may cause oily spotting bowel movements, oily stools, stomach pain, and flatulence.

Limitations of current knowledge

The limitation of drugs for obesity is that we still do not know fully the neural basis of appetite and how to modulate it. Appetite is clearly a very important instinct to promote survival. Arguably any drug that would abolish appetite may carry a high mortality risk and may be unsuitable for clinical use.

Because the human body uses various chemicals and hormones to protect its stores of fat (a reaction probably useful to our ancestors when food was scarce in the past,) there has not yet been found a 'silver bullet', or a way to completely circumvent this natural habit of protecting excess food stores. Because of this, anti-obesity drugs are not a practical long-term solution for people who are overweight.

Future developments

More recent developments may be promising in development of drugs that can combat obesity. The discovery of cannabinoid receptors in the brain, liver and muscle has stimulated research in a new class of drugs, namely cannabinoid (CB1) receptor antagonists. One such

drug in development is Rimonabant from Sanofi-Aventis, it is designed to block the effects of endogenous cannabinoids. This type of drug is particularly interesting since it not only causes weight loss but reverses the metabolic effects of obesity such as insulin resistance and hyperlipidemia. It is also interesting to note that this class of drugs may decrease the tendency to abuse substances such as alcohol and tobacco. The weight loss reported with rimonabant is modest (approximately 20 lbs.), although it is unlikely that this drug will successfully treat morbid obesity. It promises to be very useful in treating modest obesity and reversing some of the metabolic complications of this condition.

Reference

- Snow V, Barry P, Fitterman N, Qaseem A, Weiss K; Clinical Efficacy Assessment Subcommittee of the American College of Physicians. Pharmacologic and surgical management of obesity in primary care: a clinical practice guideline from the American College of Physicians. Ann Intern Med 2005;142:525-31. Fulltext. PMID 15809464.

Anorectics

Anorectics, *anorexigenics* or *appetite suppressants* are drugs that reduce the desire to eat ("anorectic", from the Greek an- = "not" and oreg- = "extend, reach").

("Anorectic" is also a term for an anorexic person, a person suffering from Anorexia nervosa.) Compare to "anorexic" alone which simply means, "without appetite". By contrast, anorexia nervosa is a mental disorder regarding the loss of appetite.

History and initial uses

Used on a short term basis clinically to treat obesity, some appetite suppressants are also available over the counter. Drugs of this class are frequently stimulants of the phenethylamine family, related to Amphetamine (speed). Amphetamines were widely issued to British soldiers during the First World War in order to suppress their appetites and thus ease the strain on the over-stretched logistics network.

The German military experimented with a similar system in 1945, when food supplies were very short in Germany. Following the Second World War, amphetamines were re-directed for use on the civilian market. Indeed, amphetamine itself was sold commercially as an appetite suppressant until it was outlawed in most parts of the world in the late 1950s due to increasing exploitation of its stimulant properties ("abuse"). Many Amphetamine produce side effects including addiction, tachycardia and hypertension, making prolonged unsupervised use dangerous.

Public health concerns

Epidemics of fatal pulmonary hypertension and heart valve damage associated with anorectic agents have led to the withdrawal of products from the market. This was the case with aminorex in the 1960s, and again in the 1990s with fenfluramine (see: Fen-phen). Likewise, association of the related appetite suppressant phenylpropanolamine with hemorrhagic stroke led the Food and Drug Administration (FDA) to request its withdrawal from the market in the United States in 2000, and similar concerns regarding Ephedrine resulted in an FDA ban on its inclusion in dietary supplements, in 2004.

Currently marketed appetite suppressants

In spite of these precedents, numerous related compounds are still marketed today as appetite suppressants. These include:

- Phentermine (Fastin®, Adipex®, Ionamin® and others)
- Diethylpropion (Tenuate®)
- Phendimetrazine (Prelu-2®, Bontril®)
- Benzphetamine (Didrex®)
- Sibutramine (Meridia®, Reductil®) is a recent addition, which is used with orlistat by doctors to control obesity
- Rimonabant (Acomplia®), a cannabinoid receptor antagonist that will be available in 2006
- Oxyntomodulin
- Fluoxetine hydrochloride (Prozac)

and others.

See also

- Amphetamine
- Stimulant
- Phenethylamine
- Fen-phen
- Ephedrine

Fen-phen

Fen-phen was an anti-obesity medication (an anorectic) which consisted of two drugs: fenfluramine and phentermine. Fenfluramine, and later a related drug, dexfenfluramine, was marketed by American Home Products, now known as Wyeth.

After reports of valvular heart disease and pulmonary hypertension primarily in women who had been undergoing treatment with fen-phen, the Food and Drug Administration (FDA) requested its withdrawal from the market in September 1997.

The action was based on findings from doctors who had evaluated patients taking these two drugs with echocardiograms, a special procedure that can test the functioning of heart valves. These findings indicated that approximately 30 percent of patients who were evaluated had abnormal echocardiograms, even though they had no symptoms. This is a much higher than expected percentage of abnormal test results.

In July 1997, researchers at the Mayo Clinic and Mayo Foundation reported 24 cases of rare valvular disease in women who took the "fen-phen" combination therapy. FDA alerted medical doctors that it had received nine additional reports of the same type, and requested all health care professionals to report any such cases to the agency's MedWatch program or to the respective pharmaceutical manufacturers.

Subsequently, FDA received 66 additional reports of heart valve disease associated mainly with "fen-phen." There were also reports of cases seen in patients taking only fenfluramine or dexfenfluramine. FDA requested that the manufacturers of fenfluramine and dexfenfluramine stress the potential risk to the heart in the drugs' labeling and patient package inserts. As of 1997, the FDA continued to receive reports of cardiac valvular disease in persons who have taken these drugs.

As of 2004, fen-phen is no longer widely available. In April 2005, American Lawyer magazine ran a cover story on the fen-phen mass tort crisis and reported that more than 50,000 product liability lawsuits had been filed by alleged fen-phen victims. Estimates of total liability run as high as $14 billion.

Ephedra

Species of *Ephedra* have traditionally been used by indigenous people for a variety of medicinal purposes, and are a likely candidate for the Soma plant of Indo-Iranian religion. Also known as *ma huang*, it was used in Traditional Chinese Medicine up to 5,000 years ago for the treatment of asthma and hay fever, as well as for the common cold.[1].

In recent years attention has been focussed on the safety of ephedra by the Food & Drug Administration and critics in the biomedical community due to the use of the herb as a stimulant and a dieting aid. As a result of adverse effects of ephedra overdose to the cardiovascular system, Western medical professionals recommend against the consumption of any ephedra.[2] Despite these warnings, ephedra is a safe herbal medicine when prescribed in appropriate doses by trained practitioners of Traditional Chinese Medicine[3].

Chemistry

The alkaloids Ephedrine and pseudoephedrine are the active constituents of the plant. Pseudoephedrine is used in over-the-counter decongestants. Ephedrine is used to treat low blood pressure, but alternatives with reduced cardiovascular risk have replaced it for treating asthma. It is also considered a performance-enhancing drug and is prohibited in

most competitive sports. Some species in the Ephedra genus have zero alkaloid content and are therefore essentially inert, however the most commonly used species, Ephedra sinica, has a total alkaloid content of 1–3% by dry weight. Ephedrine constitutes 40–90% of the alkaloid content, with the remainder consisting of pseudoephedrine and the demethylated forms of each [4].

Effects

Ephedra is both a stimulant (similar to adrenaline) and a thermogenic. It stimulates the brain, increases heart rate, constricts blood vessels (increasing blood pressure), and expands bronchial tubes (making breathing easier). Its thermogenic properties cause an increase in metabolism, evidenced by an increase in body heat.

In traditional Chinese herbology, ephedra is most notably included in many herbal formulas that treat cold and flu such as ma huang tang (ephedra decoction) or ma xing shi gan tang (ephedra, apricot kernel, gypsum, and licorice decoction). Ephedra is used therapeutically as a diaphoretic to help expel exterior pathogens and regulate the proper functioning of the lung.[5].

Side effects of ephedra overdose may include irritability, nervousness, dizziness, trembling, headache, insomnia, profuse perspiration, dehydration, itchy scalp and skin, vomiting and hyperthermia.

Safety

Just like other stimulants such as Ritalin[6], in high doses ephedra can cause heart attacks, stroke, and seizures[7]. The sale of ephedra is now regulated by the FDA due to the abuse of the herb by dieters and athletes who take it in excessively large doses with the intent of losing weight and enhancing athletic performance.

The FDA maintains that "[ephedra] is dangerous at any dose"[8]. But there are many people including experienced users of ephedra[9] who don't agree with the FDA. One popular website with a focus on ephedra questions the FDA's recommendation, asking, "If ephedra is as dangerous as the FDA claims it is, given that the Chinese have been using it for 5,000 years, shouldn't they have experienced enough adverse events to be wary of it? If the FDA is so forceful in its opinion that any amount of natural ephedra is harmful, why does it allow you to buy Big Pharma's synthetic versions of ephedra, 240mg pseudoephedrine[10] and 25mg ephedrine[11] without a prescription? Unless natural ephedra is more dangerous than its synthetic form, it's disingenuous to prohibit the sale of natural ephedra if the synthetic form can be sold without a prescription!"[12]

Ephedra and pseudoephedrine are precursors to methamphetamine. After ephedra was restricted, sales of pseudoephedrine soared (which can be used instead of ephedra in the production of the drug methamphetamine). Sales of decongestants such as Sudafed now have restrictions and are monitored in the United States. However it should be stated that decongestants were popular for the making of methamphetamine prior to the restrictions placed on ephedral products.

Regulatory history in the United States

Beginning in the 1990s, concerns about the safety of Ephedra and Ephedra-based products began to be publicly raised in the United States. Concentrated mixtures were found in weight control products marketed as "dietary supplements". Sympathomimetic amines such as ephedrine raise heart rate and blood pressure and can be particularly hazardous to those with pre-existing cardiac problems. After receiving over 800 reports of "adverse events", the country's federal Food and Drug Administration (FDA) proposed regulations in 1997 for a warning label, and a limited dose of 8mg (no more than 24mg per day).[13]

After various petitions for and against the regulations, (including complaints about the accuracy of dosage and lack of quality control in the dietary supplement industry [14]) the FDA hired the RAND Corporation to do a study in 2002, [15] and eventually linked 155 deaths to Ephedra, most of them caused by cardiac problems and strokes.

In May 2003, the health food store General Nutrition Center announced that they would stop carrying ephedra-containing products as of June 2003. [12]

The FDA must approve all drugs before they may be sold in the United States. It considers the risks and benefits of medications for specific medical conditions, may require a doctor's prescription, make labeling requirements, or ban the drug entirely. The burden of proof for safety is on the manufacturer. The Dietary Supplement Health and Education Act of 1994 creates a class of substances known as dietary supplements, which are not subject to pre-approval, and for which the burden of proof is on the government if it wishes to restrict availability. As a traditional herb, Ephedra qualifies as a dietary supplement.

On December 30, 2003, the FDA announced a ban (effective 12 April 2004) on the uncontrolled sale of dietary supplements containing Ephedra, citing "an unreasonable risk of illness or injury" from the use of the drug. The active ingredients ephedrine and pseudoephedrine remained available as an ingredient in some over the counter (OTC) medications that are clearly labeled in accordance with FDA regulations. Chemicals created in a laboratory do not qualify as dietary supplements, even if they are the same as those found in natural products.

Many advocates maintained that Ephedra was safe in low doses typical of traditional herbal preparations, and that the adverse cardiovascular effects were associated with higher doses.

The Nutraceutical Corporation of Park City, Utah, which had been selling a relatively low dose (10mg, compared to 40mg-100mg doses also on the market) sued the FDA. On 14 April 2005, Utah federal district judge Tena Campbell ruled in favor of the company.[16] The ruling stated that because of the 1994 law and Ephedra's status as a dietary supplement, the FDA did not have the statutory authority to require the manufacturer to prove that the product offered a benefit, and that it had failed to meet its burden of proof that the 10mg dose posed a sufficient risk. Nutraceutical said that it did not plan to re-introduce Ephedra, and that it had brought the suit merely to protect its other product lines from overzealous regulation by the FDA. The FDA said that it considered further research into the dose-dependent safety of Ephedra to be unethical, given the lack of benefit (other than for short-term weight loss [17]) and potential risk.[18] Critics renewed calls to reform the 1994 dietary supplement law.[19][20]

The state of California has reinstated Ephedra dietary supplements in January 2006, followed by New York and Illinois. These laws are not affected by the federal court decision. [21]

On August 17, 2006 a three judge panel of the United States Court of Appeals for the Tenth Circuit overruled a lower United States District Court decision by Judge Tena Campbell for the District of Utah. [22]

On August 18, 2006, Jonathan Emord, the attorney representing Nutraceutical Corporation announced "On or before September 29, 2006, Plaintiff Nutraceutical Corporation will file a petition for rehearing en banc by the entire 10th Circuit." [23]

In professional sports

In the 1994 FIFA World Cup, the Argentine footballer Diego Armando Maradona tested positive for ephedrine in a doping control for using one dietary supplement product containing the substance. The Japanese motorcycle racer Noriyuki Haga tested positive for it in 2000, being disqualified from two races and banned from two more as a result.

The U.S. National Football League banned players from using ephedra as a dietary supplement in 2001 after the death of Minnesota Vikings offensive tackle Korey Stringer. The substance is also banned by the National Basketball Association.[24]

Baseball pitcher Steve Bechler of the Baltimore Orioles died in 2003 after taking the supplement that same year. [13] Later that year, his widow filed a $600 million wrongful death lawsuit against the manufacturer.[25]

NFL player Todd Sauerbrun of the Denver Broncos was suspended for the first month of the 2006 season after testing positive for the banned supplement ephedra.

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Antiparkinsonian agents

Parkinson's disease
Classifications and external resources

ICD-10

G20.

ICD-9

332

DiseasesDB

9651

MedlinePlus

000755

eMedicine

neuro/304 neuro/635 **in young**
pmr/99 **rehab**

Parkinson's disease (also known as *Parkinson disease* or *PD*) is a degenerative disorder of the central nervous system that often impairs the sufferer's motor skills and speech.

Parkinson's disease belongs to a group of conditions called movement disorders. It is often characterized by muscle rigidity, tremor, a slowing of physical movement (bradykinesia), and in extreme cases, a loss of physical movement (akinesia). The primary symptoms are the results of excessive muscle contraction, normally caused by the insufficient formation and action of dopamine, which is produced in the dopaminergic neurons of the brain. Secondary symptoms may include high level cognitive dysfunction and subtle language problems. PD is both chronic, meaning it persists over a long period of time, and progressive.

PD is the most common cause of parkinsonism, a group of similar symptoms. PD is also called "primary parkinsonism" or "idiopathic PD" ("idiopathic" meaning of no known cause). While most forms of parkinsonism are idiopathic, there are some cases where the symptoms may result from toxicity, drugs, genetic mutation, head trauma, or other medical disorders.

History

Symptoms of Parkinson's disease have been known and treated since ancient times.[1] However, it was not formally recognised and its symptoms were not documented until 1817 in An Essay on the Shaking Palsy[2] by the British physician James Parkinson. Parkinson's disease was then known as paralysis agitans. The underlying biochemical changes in the brain were identified in the 1950s, due largely to the work of Swedish scientist Arvid Carlsson who later went on to win a Nobel Prize. L-dopa entered clinical practice in 1967[3], and the first study reporting improvements in patients with Parkinson's disease resulting from treatment with L-dopa was published in 1968.[4]

Symptoms

Parkinson disease affects movement (motor symptoms). Typical other symptoms include disorders of mood, behavior, thinking, and sensation (non-motor symptoms). Individual patients' symptoms may be quite dissimilar; progression is also distinctly individual.

Motor symptoms

The cardinal symptoms are:

- tremor: normally 4-7Hz tremor, maximal when the limb is at rest, and decreased with voluntary movement. It is typically unilateral at onset. This is the most apparent and well-known symptom, though an estimated 30% of patients have little perceptible tremor; these are classified as akinetic-rigid.
- rigidity: stiffness; increased muscle tone. In combination with a resting tremor, this produces a ratchety, "cogwheel" rigidity when the limb is passively moved.
- bradykinesia/akinesia: respectively, slowness or absence of movement. Rapid, repetitive movements produce a dysrhythmic and decremental loss of amplitude. Also "dysdiadokinesia", which is the loss of ability to perform rapid alternating movements
- postural instability: failure of postural reflexes, which leads to impaired balance and falls.

Other motor symptoms include:

- Gait and posture disturbances:
    - Shuffling: gait is characterized by short steps, with feet barely leaving the ground, producing an audible shuffling noise. Small obstacles tend to trip the patient
    - Decreased arm swing: a form of bradykinesia
    - Turning "en bloc": rather than the usual twisting of the neck and trunk and pivoting on the toes, PD patients keep their neck and trunk rigid, requiring multiple small steps to accomplish a turn.
    - Stooped, forward-flexed posture. In severe forms, the head and upper shoulders may be bent at a right angle relative to the trunk (camptocormia).

- Festination: a combination of stooped posture, imbalance, and short steps. It leads to a gait that gets progressively faster and faster, often ending in a fall.
- Gait freezing: "freezing" is another word for akinesia, the inability to move. Gait freezing is characterized by inability to move the feet, especially in tight, cluttered spaces or when initiating gait.
- Dystonia (in about 20% of cases): abnormal, sustained, painful twisting muscle contractions, usually affecting the foot and ankle, characterized by toe flexion and foot inversion, interfering with gait. However, dystonia can be quite generalized, involving a majority of skeletal muscles; such episodes are acutely painful and completely disabling.

- Speech and swallowing disturbances
  - Hypophonia: soft speech. Speech quality tends to be soft, hoarse, and monotonous.
  - Festinating speech: excessively rapid, soft, poorly-intelligible speech.
  - Drooling: most likely caused by a weak, infrequent swallow and stooped posture.
  - Non-motor causes of speech/language disturbance in both expressive and receptive language: these include decreased verbal fluency and cognitive disturbance especially related to comprehension of emotional content of speech and of facial expression[5]
  - Dysphagia: impaired ability to swallow. Can lead to aspiration, pneumonia, and ultimately death.
- Other motor symptoms:
  - fatigue (up to 50% of cases);
  - masked facies (a mask-like face also known as hypomimia), with infrequent blinking;[6]
  - difficulty rolling in bed or rising from a seated position;
  - micrographia (small, cramped handwriting);
  - impaired fine motor dexterity and coordination;
  - impaired gross motor coordination;
  - Poverty of movement: overall loss of accessory movements, such as decreased arm swing when walking, as well as spontaneous movement.

Non-motor symptoms

Mood disturbances

- Estimated prevalence rates of depression vary widely according to the population sampled and methodology used. Reviews of depression estimate its occurrence in anywhere from 20-80% of cases.[7] Estimates from community samples tend to find lower rates than from specialist centres. Most studies use self-report questionnaires such as the Beck Depression Inventory which may

overinflate scores due to physical symptoms. Studies using diagnostic interviews by trained psychiatrists also report lower rates of depression.

- More generally, there is an increased risk for any individual with depression to go on to develop Parkinson's disease at a later date.[8]
- Seventy percent of individuals with Parkinson's disease diagnosed with pre-existing depression go on to develop anxiety. Ninety percent of Parkinson's disease patients with pre-existing anxiety subsequently develop depression); apathy or abulia.

Cognitive disturbances

- slowed reaction time; both voluntary and involuntary motor responses are significantly slowed.
- executive dysfunction, characterized by difficulties in: differential allocation of attention, impulse control, set shifting, prioritizing, evaluating the salience of ambient data, interpreting social cues, and subjective time awareness. This complex is present to some degree in most Parkinson's patients; it may progress to:
- dementia: a later development in approximately 20-40% of all patients, typically starting with slowing of thought and progressing to difficulties with abstract thought, memory, and behavioral regulation.
- memory loss; procedural memory is more impaired than declarative memory. Prompting elicits improved recall.
- medication effects: some of the above cognitive disturbances are improved by dopaminergic medications, while others are actually worsened [9]

Sleep disturbances

- Excessive daytime somnolence;
- Initial, intermediate, and terminal insomnia;
- Disturbances in REM sleep: disturbingly vivid dreams, and REM Sleep Disorder, characterized by acting out of dream content;

Sensation disturbances

- impaired visual contrast sensitivity, spatial reasoning, colour discrimination, convergence insufficiency (characterized by double vision) and oculomotor control
dizziness and fainting; usually attributable orthostatic hypotension, a failure of the autonomous nervous system to adjust blood pressure in response to changes in body position

- impaired proprioception (the awareness of bodily position in three-dimensional space)
- reduction or loss of sense of smell (microsmia or anosmia),
- pain: neuropathic, muscle, joints, and tendons, attributable to tension, dystonia, rigidity, joint stiffness, and injuries associated with attempts at accommodation

Autonomic disturbances

- oily skin and seborrheic dermatitis
- urinary incontinence, typically in later disease progression
- constipation and gastric dysmotility that is severe enough to endanger comfort and even health
- altered sexual function: characterized by profound impairment of sexual arousal, behavior, orgasm, and drive is found in mid and late Parkinson disease. Current data addresses male sexual function almost exclusively
- weight loss, which is significant over a period of ten years - 8% of body weight lost compared with 1% in a control group.

Diagnosis

There are currently no blood or laboratory tests that have been proven to help in diagnosing sporadic PD. Therefore the diagnosis is based on medical history and a neurological examination. The disease can be difficult to diagnose accurately. The Unified Parkinson's Disease Rating Scale is the primary clinical tool used to assist in diagnosis and determine severity of PD. Indeed, only 75% of clinical diagnoses of PD are confirmed at autopsy[10]. Early signs and symptoms of PD may sometimes be dismissed as the effects of normal aging. The physician may need to observe the person for some time until it is apparent that the symptoms are consistently present. Usually Doctors look for shuffling of feet and lack of swing in the arms. Doctors may sometimes request brain scans or laboratory tests in order to rule out other diseases. However, CT and MRI brain scans of people with PD usually appear normal.

Descriptive epidemiology

Parkinson's disease is widespread, with a prevalence estimated between 100 and 250 cases per 100,000 in North America; globally prevalence estimates range from a low of 15 per 100,000 in China to a high of 657 per 100,000 in Argentina. Because prevalence rates can be affected by socio-ecomically driven differences in survival as well as biased by survey technique problems [11] , incidence is a more sensitive indicator: rates have ranged from 1.5 per 100,000 in China to a high of 14.8 per 100,000 in Finland.[12] Incidence has been estimated by several groups. A study carried out in northern California[13] observed an age and sex corrected incidence of 13.4 per 100,000/year. The study authors noted a rapid increase in incidence with age, male rates nearly double female rates, and an elevated rate

amongst Hispanics. A study in Spain[14] (of a population of people aged 65 to 85) calculated incidence, adjusted for age and sex, of 186.8/100,000 per year, with men's rates being 2.55 times that of women. For the same age group, the northern California study observed an incidence of roughly 120/100,000/year. A Dutch study[15], published in the same year, noted age-specific incidence rates from 0.3 per 1000 person-years in subjects aged 55 to 65 years, to 4.4 per 1000 person-years for those aged e85 year, and a sex ratio of 1.55 for male incidence.

Cases of PD are reported at all ages, though it is quite rare in people younger than 40 and the average age at which symptoms begin is 58-60; it is principally a disease of the elderly. It occurs in all parts of the world, but appears to be more common in people of European ancestry than in those of African ancestry. Those of East Asian ancestry have an intermediate risk. It is more common in rural than urban areas and men are affected slightly more often than women. It is highly unusual for people under 40 to develop Parkinson's Disease, and twin studies (Tanner)[16]. have shown such disease to be almost entirely genetically caused.

Related diseases

There are other disorders that are called Parkinson-plus diseases. These include:

- Multiple system atrophy (MSA)
  - Shy-Drager syndrome (SDS)
  - Striatonigral degeneration (SND)
  - Olivopontocerebellar atrophy (OPCA)
- Progressive supranuclear palsy (PSP)
- Corticobasal degeneration (CBD)

Some people include dementia with Lewy bodies (DLB) as one of the 'Parkinson-plus' syndromes. Although idiopathic Parkinson's disease patients also have Lewy bodies in their brain tissue, the distribution is denser and more widespread in DLB. Even so, the relationship between Parkinson disease, Parkinson disease with dementia (PDD) and dementia with Lewy bodies (DLB) might be most accurately conceptualized as a spectrum, with a discrete area of overlap between each of the three disorders. The natural history and role of Lewy bodies is very little understood.

Patients often begin with typical Parkinson's disease symptoms which persist for some years; these Parkinson-plus diseases can only be diagnosed when other symptoms become apparent with the passage of time. These Parkinson-plus diseases usually progress more quickly than typical ideopathic Parkinson disease. The usual anti-Parkinson's medications are typically either less effective or not effective at all in controlling symptoms; patients may be exquisitely sensitive to neuroleptic medications like haloperidol. Additionally, the cholinesterase inhibiting medications have shown preliminary efficacy in treating the cognitive, psychiatric, and behavioral aspects of the disease, so correct differential diagnosis is important.

Wilson's disease (hereditary copper accumulation) may present with parkinsonistic features; young patients presenting with parkinsonism may be screened for this rare condition. Essential tremor is often mistaken for Parkinson's disease but usually lacks all features besides tremor.

Pathology

The symptoms of Parkinson's disease result from the loss of pigmented dopamine-secreting (dopaminergic) cells and subsequent loss of melanin, secreted by the same cells, in the pars compacta region of the substantia nigra (literally "black substance"). These neurons project to the striatum and their loss leads to alterations in the activity of the neural circuits within the basal ganglia that regulate movement, in essence an inhibition of the direct pathway and excitation of the indirect pathway.

The direct pathway facilitates movement and the indirect pathway inhibits movement, thus the loss of these cells leads to a hypokinetic movement disorder. The lack of dopamine results in increased inhibition of the ventral lateral nucleus of the thalamus, which sends excitatory projections to the motor cortex, thus leading to hypokinesia.

There are four major dopamine pathways in the brain; the nigrostriatal pathway, referred to above, mediates movement and is the most conspicuously affected in early Parkinson's disease. The other pathways are the mesocortical, the mesolimbic, and the tuberoinfundibular. These pathways are associated with, respectively: volition and emotional responsiveness; desire, initiative, and reward; and sensory processes and maternal behavior. Disruption of dopamine along the non-striatal pathways likely explains much of the neuropsychiatric pathology associated with Parkinson's disease.

The mechanism by which the brain cells in Parkinson's are lost may consist of an abnormal accumulation of the protein alpha-synuclein bound to ubiquitin in the damaged cells. The alpha-synuclein-ubiquitin complex cannot be directed to the proteosome. This protein accumulation forms proteinaceous cytoplasmic inclusions called Lewy bodies. Latest research on pathogenesis of disease has shown that the death of dopaminergic neurons by alpha-synuclein is due to a defect in the machinery that transports proteins between two major cellular organelles — the endoplasmic reticulum (ER) and the Golgi apparatus. Certain proteins like Rab1 may reverse this defect caused by alpha-synuclein in animal models.[17]

Excessive accumulations of iron, which are toxic to nerve cells, are also typically observed in conjunction with the protein inclusions. Iron and other Transition metals such as copper bind to neuromelanin in the affected neurons of the Substantia nigra. So, neuromelanin may be acting as a protective agent. Alternately, neuromelanin (an electronically active semiconductive polymer) may play some other role in neurons.[18] That is, coincidental excessive accumulation of transition metals, etc. on neuromelanin may figure in the differential dropout of pigmented neurons in Parkinsonism. The most likely mechanism is generation of Reactive oxygen species.[19]

Iron induces aggregation of synuclein by oxidative mechanisms.[20] Similarly, dopamine and the byproducts of dopamine production enhance alpha-synuclein aggregation. The precise mechanism whereby such aggregates of alpha-synuclein damage the cells is not known. The aggregates may be merely a normal reaction by the cells as part of their effort to correct a different, as-yet unknown, insult. Based on this mechanistic hypothesis, a transgenic mouse model of Parkinson's has been generated by introduction of human wild-type ±-synuclein into the mouse genome under control of the platelet-derived-growth factor-^{2} promoter. [21]

Causes of Parkinson's disease

Most people with Parkinson's disease are described as having idiopathic Parkinson's disease (having no specific cause). There are far less common causes of Parkinson's disease including genetic, toxins, head trauma, and drug-induced Parkinson's disease.

Genetic

In recent years, a number of specific genetic mutations causing Parkinson's disease have been discovered, including in certain populations (Contursi, Italy). These account for a small minority of cases of Parkinson's disease. Somebody who has Parkinson's disease is more likely to have relatives that also have Parkinson's disease. However, this does not mean that the disorder has been passed on genetically.

Genetic forms that have been identified include:

external links in this section are to OMIM

- PARK1 (OMIM #168601), caused by mutations in the SNCA gene, which codes for the protein alpha-synuclein. PARK1 causes autosomal dominant Parkinson disease. So-called PARK4 is probably caused by triplication of SNCA.[22]
- PARK2 (OMIM *602544), caused by mutations in protein parkin. Parkin mutations may be one of the most common known genetic causes of early-onset Parkinson disease. In one study, of patients with onset of Parkinson disease prior to age 40 (10% of all PD patients), 18% had parkin mutations, with 5% homozygous mutations.[23] Patients with an autosomal recessive family history of parkinsonism are much more likely to carry parkin mutations if age at onset is less than 20 (80% vs. 28% with onset over age 40).[24]Patients with parkin mutations (PARK2) do not have Lewy bodies. Such patients develop a syndrome that closely resembles the sporadic form of PD; however, they tend to develop symptoms at a much younger age.
- PARK3 (OMIM %602404), mapped to 2p, autosomal dominant, only described in a few kindreds.
- PARK5, caused by mutations in the UCHL1 gene (OMIM +191342) which codes for the protein ubiquitin carboxy-terminal hydrolase L1
- PARK6 (OMIM #605909), caused by mutations in PINK1 (OMIM *608309) which codes for the protein PTEN-induced putative kinase 1.
- PARK7 (OMIM #606324), caused by mutations in DJ-1 (OMIM 602533)
- PARK8 (OMIM #607060), caused by mutations in LRRK2 which codes for the protein dardarin. In vitro, mutant LRRK2 causes protein aggregation and cell death, possibly through an interaction with parkin.[25] LRRK2 mutations, of which the most common is G2019S, cause autosomal dominant Parkinson disease, with a penetrance of nearly 100% by age 80.[26] G2019S is the most common known genetic cause of Parkinson disease, found in 1-6% of U.S. and

European PD patients.[27] It is especially common in Ashkenazi Jewish patients, with a prevalence of 29.7% in familial cases and 13.3% in sporadic.[28]

- PARK12 (OMIM %300557), maps to the X chromosome

Toxins

One theory holds that the disease may result in many or even most cases from the combination of a genetically determined vulnerability to environmental toxins along with exposure to those toxins.[29] This hypothesis is consistent with the fact that Parkinson's disease is not distributed homogenously throughout the population: rather, its incidence varies geographically. It would appear that incidence varies by time as well, for although the later stages of untreated PD are distinct and readily recognizable, the disease was not remarked upon until the beginnings of the Industrial Revolution, and not long thereafter become a common observation in clinical practice. The toxins most strongly suspected at present are certain pesticides and transition-series metals such as manganese or iron, especially those that generate reactive oxygen species,[19] [30] and or bind to neuromelanin, as originally suggested by G.C. Cotzias. [31] [32] MPTP is used as a model for Parkinson's as it can rapidly induce parkinsonian symptoms in human beings and other animals, of any age. MPTP was notorious for a string of Parkinson's disease cases in California in 1982 when it contaminated the illicit production of the synthetic opiate MPPP. Its toxicity likely comes from generation of reactive oxygen species. [33]

Other toxin-based models employ PCBs,[34] paraquat[35] (a herbicide) in combination with maneb (a fungicide) [36] rotenone[37] (an insecticide), and specific organochlorine pesticides including dieldrin[38] and lindane.[39] Numerous studies have found an increase in Parkinson disease in persons who consume rural well water; researchers theorize that water consumption is a proxy measure of pesticide exposure. In agreement with this hypothesis are studies which have found a dose-dependent an increase in PD in persons exposed to agricultural chemicals.

Almost all of the PD-causing toxins act on the mitochondrial complex I of the electron transfer chain, and sporadic PD cases have been found to have a partial loss of activity of this enzyme complex. Studies in cybrids have found that mitochondrial DNA, rather than nuclear DNA, is responsible for the dysfunction. Most recently, microheteroplasmic mutations in one of the mitochondrial complex I genes, ND5, were found to be sufficient to diagnose sporadic PD correctly in 27 out of 28 cases. While additional studies are needed, mitochondrial microheteroplasmic mutations may be the cause of the majority of PD cases.

However, the ubiquity of agricultural chemical exposures makes it difficult to gauge the true extent of the problem. In the current state of knowledge about the origins of the disease, it appears that family history of the disease and (especially) multiple episodes of head-trauma-induced unconsciousness increase individual risk more than does pesticide exposure, but research is continuing.

Head trauma

Past episodes of head trauma are reported more frequently by sufferers than by others in the population.[40][41][42] A methodologically strong recent study[40] found that those who have experienced a head injury are four times more likely to develop Parkinson’s disease than those who have never suffered a head injury. The risk of developing Parkinson’s increases eightfold for patients who have had head trauma requiring hospitalization, and it

increases 11-fold for patients who have experienced severe head injury. The authors comment that since head trauma is a rare event, the contribution to PD incidence is slight. They express further concern that their results may be biased by recall, i.e., the PD patients because they reflect upon the causes of their illness, may remember head trauma better than the non-ill control subjects.

These limitations were overcome recently by Tanner and colleagues [43], who found a similar risk of 3.8, with increasing risk associated with more severe injury and hospitalization.

Drug-induced

Antipsychotics, which are used to treat schizophrenia and psychosis, can induce the symptoms of Parkinson's disease (or parkinsonism) by lowering dopaminergic activity. Due to feedback inhibition, L-dopa can also eventually cause the symptoms of Parkinson's disease that it initially relieves. Dopamine agonists can also eventually contribute to Parkinson's disease symptoms by increasing the sensitivity of dopamine receptors.

Treatment

Parkinson's disease is a chronic disorder that requires broad-based management including patient and family education, support group services, general wellness maintenance, exercise, and nutrition. At present, there is no cure for PD, but medications or surgery can provide relief from the symptoms.

Levodopa

The most widely used form of treatment is L-dopa in various forms. L-dopa is transfomed into dopamine in the dopaminergic neurons by L-aromatic amino acid decarboxylase (often known by its former name dopa-decarboxylase). However, only 1-5% of L-DOPA enters the dopaminergic neurons. The remaining L-DOPA is often metabolised to dopamine elsewhere, causing a wide variety of side effects. Due to feedback inhibition, L-dopa results in a reduction in the endogenous formation of L-dopa, and so eventually becomes counterproductive.

Carbidopa and benserazide are dopa decarboxylase inhibitors. They help to prevent the metabolism of L-dopa before it reaches the dopaminergic neurons and are generally given as combination preparations of carbidopa/levodopa (co-careldopa) (e.g. Sinemet, Parcopa) and benserazide/levodopa (co-beneldopa) (e.g. Madopar). There are also controlled release versions of Sinemet and Madopar that spread out the effect of the L-dopa. Duodopa is a combination of levodopa and carbidopa, dispersed as a viscous gel. Using a patient-operated portable pump, the drug is continuously delivered via a tube directly into the upper small intestine, where it is rapidly absorbed.

Talcopone inhibits the COMT enzyme, thereby prolonging the effects of L-dopa, and so has been used to complement L-dopa. However, due to its possible side effects such as liver failure, it's limited in its availability.

A similar drug, entacapone, has similar efficacy and has not been shown to cause significant alterations of liver function. A recent follow-up study by Cilia and colleagues looked at the clinical effects of long-term administration of entacapone on motor performance and pharmacological compensation is advanced PD patients with motor fluctuations. 47 patients with advanced PD and motor fluctuations were followed for six years from the first prescription of entacapone and showed a stabilization of motor conditions, reflecting entacapone can maintain adequate inhibition of COMT over time [44].

Mucuna pruriens, is a natural source of therapeutic quantities of L-dopa.

Dopamine agonists

The dopamine-agonists bromocriptine (Parlodel), pergolide (Permax), pramipexole (Mirapex), ropinirole (Requip), cabergoline (Cabaser), apomorphine (Apokyn), and lisuride (Revanil), are moderately effective. These have their own side effects including those listed above in addition to somnolence, hallucinations and /or insomnia. Dopamine agonists initially act by stimulating some of the dopamine receptors. However, they cause the dopamine receptors to become progressively less sensitive, thereby eventually increasing the symptoms.

Dopamine agonists can be useful for patients experiencing on-off fluctuations and dyskinesias as a result of high doses of L-dopa. Apomorphine can be administered via subcutaneous injection using a small pump which is carried by the patient. A low dose is automatically administered throughout the day, reducing the fluctuations of motor symptoms by providing a steady dose of dopaminergic stimulation. After an initial "apomorphine challenge" in hospital to test its effectiveness and brief patient and caregiver, the primary caregiver (often a spouse or partner) takes over maintenance of the pump. The injection site must be changed daily and rotated around the body to avoid the formation of nodules. Apomorphine is also available in a more acute dose as an autoinjector pen for emergency doses such as after a fall or first thing in the morning.

MAO-B inhibitors

Selegiline (Eldepryl) and rasagiline (Azilect) reduce the symptoms by inhibiting monoamine oxidase-B (MAO-B), which inhibits the breakdown of dopamine secreted by the dopaminergic neurons. By-products of selegiline include amphetamine and methamphetamine, which can cause side effects such as insomnia. Use of L-dopa in conjunction with selegiline has increased mortality rates that have not been effectively explained. Another side effect of the combination can be stomatitis. One report raised concern about increased mortality when MAO-B inhibitors were combined with L-dopa [45]; however subsequent studies have not confirmed this finding[46]. Unlike other non selective monoamine oxidase inhibitors, tyramine-containing foods do not cause a hypertensive crisis.

Surgical interventions

Treating PD with surgery was once a common practice. But after the discovery of levodopa, surgery was restricted to only a few cases. Studies in the past few decades have led to great improvements in surgical techniques, and surgery is again being used in people with advanced PD for whom drug therapy is no longer sufficient. Deep brain stimulation is presently the most used surgical means of treatment, but other surgical therapies that have shown promise include surgical lesion of the subthalamic nucleus[47] and of the internal segment of the globus pallidus, a procedure known as pallidotomy.[48].

Speech therapies

The most widely practiced treatment for the speech disorders associated with Parkinson's disease is Lee Silverman Voice Treatment (LSVT). LSVT focuses on increasing vocal loudness.[49]

A study found that an electronic device providing frequency-shifted auditory feedback (FAF) improved the clarity of Parkinson's patients' speech.[50]

Physical exercise

Regular physical exercise and/or therapy, including in forms such as yoga, tai chi, and dance can be beneficial to the patient for maintaining and improving mobility, flexibility, balance and a range of motion.

Methods undergoing evaluation

Gene therapy

Currently under investigation is gene therapy. This involves using a harmless virus to shuttle a gene into a part of the brain called the subthalamic nucleus (STN). The gene used leads to the production of an enzyme called glutamic acid decarboxylase (GAD), which catalyses the production of a neurotransmitter called GABA. GABA acts as a direct inhibitor on the overactive cells in the STN.

GDNF infusion involves the infusion of GDNF (glial-derived neurotrophic factor) into the basal ganglia using surgically implanted catheters. Via a series of biochemical reactions, GDNF stimulates the formation of L-dopa. GDNF therapy is still in development.

In the future, implantation of cells genetically engineered to produce dopamine or stem cells that transform into dopamine-producing cells may become available. Even these, however, will not constitute cures because they do not address the considerable loss of activity of the dopaminergic neurons.

Neuroprotective treatments

Neuroprotective treatments are at the forefront of PD research - presenting many new challenges. These agents protect neurons from cell death induced by disease presence resulting in a slower pregression of disease. Agents currently under investigation as neuroprotective agents include apoptotic drugs (CEP 1347 and CTCT346), lazaroids, bioenergetics, antiglutamatergic agents and dopamine receptors [51]

Neural transplantation

The first prospective randomised double-blind sham-placebo controlled trial of dopaminergic transplants failed to show an improvement in quality of life although some significant clinical improvements were seen in patients below the age of 60 [52]

Nutrients

Nutrients have been used in clinical studies and are widely used by people with Parkinson's disease in order to partially treat Parkinson's disease or slow down its deterioration. The L-dopa precursor L-tyrosine was shown to relieve an average of 70% of symptoms.[53] Ferrous iron, the essential cofactor for L-dopa biosynthesis was shown to relieve between 10% and 60% of symptoms in 110 out of 110 patients.[54][55]

More limited efficacy has been obtained with the use of THFA, NADH, and pyridoxine—coenzymes and coenzyme precursors involved in dopamine biosynthesis[56]. Vitamin C and vitamin E in large doses are commonly used by patients in order to theoretically lessen the cell damage that occurs in Parkinson's disease. This is because the enzymes superoxide dismutase and catalase require these vitamins in order to nullify the superoxide anion, a toxin commonly produced in damaged cells. However, in the randomized controlled trial, DATATOP of patients with early PD, no beneficial effect for vitamin E compared to placebo was seen[57]

Coenzyme Q10 has more recently been used for similar reasons. MitoQ is a newly developed synthetic substance that is similar in structure and function to coenzyme Q10. However, proof of benefit has not been demonstrated yet.

Qigong

There have been two methodologically acceptable studies looking at qigong in Parkinson's disease. In a trial in Bonn, a open-label randomised pilot study in 56 patients found an improvement in motor and non-motor symptoms amongst patients who had undergone one hour of structured Qigong exercise per week in two 8-week blocks. The authors speculate that visualizing the flow of "energy" might act as an internal cue and so help improve movement. [58]

The second study, however, found Qigong to be ineffective in treating Parkinson's disease. In that study, researchers used a randomized cross-over trial to compare aerobic training with Qigong in advanced Parkinson's disease. Two groups of PD patients were assessed, had 20 sessions of either aerobic exercise or qigong, were assessed again, then after a 2 month gap were switched over for another 20 sessions, and finally assessed again. The authors found an improvement in motor ability and cardiorespiratory function following aerobic exercise, but found no benefit following Qigong. The authors also point out that aerobic exercise had no benefit for patients' quality of life. [59]

Prognosis

PD is not by itself a fatal disease, but it does get worse with time. The average life expectancy of a PD patient is generally lower than for people who do not have the disease[60]. In the late stages of the disease, PD may cause complications such as choking, pneumonia, and falls that can lead to death.

The progression of symptoms in PD may take 20 years or more. In some people, however, the disease progresses more quickly. There is no way to predict what course the disease will take for an individual person. One commonly used system for describing how the symptoms of PD progress is called the Hoehn and Yahr scale.

Another commonly used scale is the Unified Parkinson's Disease Rating Scale (UPDRS). This much more complicated scale has multiple ratings that measure mental functioning, behavior, and mood; activities of daily living; and motor function. Both the Hoehn and Yahr scale and the UPDRS are used to measure how individuals are faring and how much treatments are helping them. It should be noted that neither scale is specific to Parkinson's Disease; that patients with other illnesses can score in the Parkinson's range.

With appropriate treatment, most people with PD can live productive lives for many years after diagnosis.

Notable Parkinson's sufferers

One famous sufferer of young-onset Parkinson's is Michael J. Fox, who has written a book about his experience of the disease and established The Michael J. Fox Foundation for Parkinson's Research to develop a cure for Parkinson's disease within this decade.

Other famous sufferers include Pope John Paul II, playwright Eugene O'Neill, artist Salvador Dalí, evangelist Billy Graham, former US Attorney General Janet Reno, boxer Muhammad Ali, dictators Adolf Hitler, Franco and Mao Zedong, and numerous actors such as Terry-Thomas, Deborah Kerr, Kenneth More, Vincent Price and Michael Redgrave.

The film Awakenings (starring Robin Williams and Robert De Niro and based on genuine cases reported by Oliver Sacks) deals sensitively and largely accurately with a similar disease, postencephalitic parkinsonism.

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Dopamine agonists

A *dopamine agonist* is a compound that activates dopamine receptors, mimicking the effect of the neurotransmitter dopamine. Some medical drugs act as dopamine agonists; they are typically used for treating Parkinson's disease, and may be useful for restless legs syndrome (RLS).

See also

- Agonist

Antiplatelet drugs

An *antiplatelet drug* is a member of a class of pharmaceuticals that decreases platelet aggregation and inhibits thrombus formation. They are effective in the arterial circulation, where anticoagulants have little effect.

They are widely used in primary and secondary prevention of thrombotic cerebrovascular or cardiovascular disease.

Choice of antiplatelet drug

A recent review [1] states: "....low-dose aspirin increases the risk of major bleeding 2-fold compared with placebo. However, the annual incidence of major bleeding due to low-dose aspirin is modest—only 1.3 patients per thousand higher than what is observed with placebo treatment. Treatment of approximately 800 patients with low-dose aspirin annually for cardiovascular prophylaxis will result in only 1 additional major bleeding episode." Further, "...the cost to prevent one major GI bleeding episode from aspirin in 1 year by substituting clopidogrel therapy would be $1,216,180..."

Antiplatelet drugs

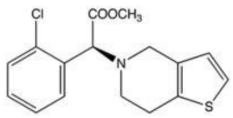
The most important antiplatelet drugs are:

- Cyclooxygenase inhibitors
  - Aspirin
- Adenosine diphosphate receptor inhibitors
  - Clopidogrel **(Plavix)**
  - Ticlopidine (Ticlid)
- Phosphodiesterase inhibitors
  - Cilostazol (Pletal)
- Glycoprotein IIB/IIIA inhibitors **(intravenous use only)**
  - Abciximab (ReoPro)
  - Eptifibatide (Integrilin)
  - Tirofiban (Aggrastat)
- Adenosine reuptake inhibitors
  - Dipyridamole (Persantine)

See also

- Anticoagulant drug

Clopidogrel (Plavix)



Systematic (IUPAC) name

(+)-(S)-methyl 2-(2-chlorophenyl)-2-(6,7-dihydrothieno[3,2-c]pyridin-5(4H)-yl)acetate

Identifiers

CAS number 113665-84-2

ATC code **B01**AC04

PubChem 60606

DrugBank APRD00444

Chemical data

Formula C***16***H***16***ClNO***2***S

Mol. weight 321.82

Pharmacokinetic data

Bioavailability >50%

Metabolism hepatic

Half life 7–8 hours (inactive metabolite)

Excretion 50% renal, 46% biliary

Therapeutic considerations

Pregnancy cat. $B1_{(AU)}$ $B_{(US)}$

Legal status $S4_{(AU)}$ $POM_{(UK)}$ $_{\text{-only(US)}}$

Routes oral

Clopidogrel is a potent oral antiplatelet agent often used in the treatment of coronary artery disease, peripheral vascular disease, and cerebrovascular disease. It is marketed by Bristol-Myers Squibb and Sanofi-Aventis under the trade name *Plavix*. It is also marketed in the generic form by Apotex, a Canadian generic pharmaceutical company, though an injunction to withhold further shipments of their form is in effect while patent issues are

dealt with. In 2005 it was the world's second highest selling pharmaceutical with sales of US$5.9 billion.

Pharmacology

The mechanism of action of clopidogrel is irreversible blockade of the adenosine diphosphate (ADP) receptor on platelet cell membranes. This receptor is named P2Y12 and is important in platelet aggregation, the cross-linking of platelets by fibrin. The blockade of this receptor inhibits platelet aggregation by blocking activation of the glycoprotein IIb/IIIa pathway.

Platelet inhibition can be demonstrated two hours after a single dose of oral clopidogrel.

Clinical use

Indications

Clopidogrel is indicated for (Rossi, 2006):

- Prevention of vascular ischaemic events in patients with symptomatic atherosclerosis
- Acute coronary syndrome without ST-segment elevation (NSTEMI), along with aspirin

It is also used, along with aspirin, for the prevention of thromboembolism after placement of intracoronary stent. (Rossi, 2006)

Most consensus-based therapeutic guidelines recommend the use of clopidogrel, over aspirin, in patients requiring antiplatelet therapy but with a history of gastric ulceration, due to the lower incidence of gastric ulceration associated with the use of clopidogrel vs aspirin. A recent study has shown that in patients with healed aspirin-induced ulcers, however, patients receiving aspirin plus the proton pump inhibitor esomeprazole had a lower incidence of recurrent ulcer bleeding than patients receiving clopidogrel. (Chan et al., 2005)

Dosage forms

Clopidogrel is marketed as *clopidogrel bisulfate* (*clopidogrel hydrogen sulfate*), most commonly under the trade name *Plavix*, as 75 mg tablets.

Adverse effects

Serious adverse drug reactions associated with clopidogrel therapy include:

- Severe neutropenia (Incidence: 5/10,000)
- Thrombotic thrombocytopenic purpura (TTP) (Incidence: 4/1,000,000 patients treated)
- Hemorrhage - The incidence of hemorrhage may be increased by the co-administration of aspirin.
    - Gastrointestinal Hemorrhage (Incidence: 2.0%)

  - Cerebral Hemorrhage (Incidence: 0.1 to 0.4%)

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Antipsychotics

The term *antipsychotic* is applied to a group of drugs used to treat psychosis. Common conditions with which antipsychotics might be used include schizophrenia, mania and delusional disorder, although antipsychotics might be used to counter psychosis associated with a wide range of other diagnoses. Antipsychotics also have some effects as mood stabilizers, leading to their frequent use in treating mood disorder (particularly bipolar disorder) even when no signs of psychosis are present. Some antipsychotics (haloperidol, pimozide) are used off-label to treat Tourette syndrome.

Antipsychotics are also referred to as *neuroleptic drugs*, or simply *neuroleptics*. The word neuroleptic is derieved from Greek. 'Neuro' refers to the nerves and 'lept' means 'to take hold of'. Thus the word means 'taking hold of one's nerves' which implies their role in mood stabilization.

There are currently two main types of antipsychotics in use, the typical antipsychotics and atypical antipsychotics. A new class of antipsychotic drugs has recently been discovered, known as dopamine partial agonists. Clinical development has progressed rapidly on partial dopamine agonists, and one drug in this class (aripiprazole) has already been approved by the Food and Drug Administration. Although the underlying mechanism of this new class is different from all previous typical and atypical antipsychotics, dopamine partial agonists are often categorized as atypicals.

Typical antipsychotics are sometimes referred to as *major tranquilizers*, due to the fact that some of them can tranquilize and sedate. This term is increasingly disused because many newer antipsychotics do not have strong sedating properties and the terminology implies a connection with benzodiazepines, whereas none exists.

Common antipsychotic drugs

Commonly used antipsychotic medications are listed below by drug group. Trade names appear in brackets.

- Typical antipsychotics:
    - Phenothiazines:
        - Chlorpromazine (Thorazine®)

        Fluphenazine (Prolixin®) - Available in decanoate (long acting) form
        Perphenazine (Trilafon®)
        Prochlorperazine (Compazine®)
        Thioridazine (Mellaril®)
        Trifluoperazine (Stelazine®)
- Butyrophenones
    - Haloperidol (Haldol®) - Available in decanoate (long acting) form
    - Droperidol

Pimozide (Orap®) - Used to treat Tourette syndrome

- Atypical antipsychotics:
  - Clozapine (Clozaril®) - Requires weekly to biweekly CBC (FBC) due to risk of agranulocytosis (a severe decrease of white blood cells).
  - Olanzapine (Zyprexa®) - Used to treat psychotic disorders including acute manic episodes and maintenance of bipolar disorder. Dosing 2.5 mg to 20 mg per day. Comes in a form that quickly dissolves in the mouth (Zyprexa Zydis). May cause appetite increase, weight gain and altered glucose metabolism leading to an increased risk of diabetes mellitus.
  - Risperidone (Risperdal®) - Dosing 0.25 to 6 mg per day and is titrated upward; divided dosing is recommended until initial titration is completed at which time the drug can be administered once daily. Available in long-acting form (Risperdal Consta that is administered every 2 weeks; usual dose is 25 mg). Comes in a form that quickly dissovles in the mouth (Risperdal M-Tab)
  - Quetiapine (Seroquel®) - Used primarily to treat bipolar disorder and schizophrenia, and "off label" to treat chronic insomnia and restless legs syndrome; it is a powerful sedative (if it's used to treat sleep disorders and is not effective at 200 mg, it is not going to be effective in this regard). Dosing starts at 25 mg and continues up to 800 mg maximum per day, depending on the severity of the symptom(s) being treated. Users typically take smaller doses during the day for the neuroleptic properties and larger dose at bedtime for the sedative effects, or divided in two equally high doses every 12 hours (75-400mg bid).
  - Ziprasidone (Geodon®) - Now (2006) approved to treat bipolar disorder. Dosing 20 mg twice daily initially up to 80 mg twice daily. Prolonged QT interval a concern; watch closely with patients who have heart disease; when used with other drugs that prolong QT interval potentially life-threatening.
- Dopamine partial agonists:
  - Aripiprazole (Abilify®) - Among the newest (2006) atypical antipsychotics; dosing 5 mg up to maximum of 30 mg has been used. Mechanism of action is thought to reduce susceptibility to metabolic symptoms seen in some other atypical antipsychotics.
  - Under clinical development - Bifeprunox; norclozapine (ACP-104).
- Other options
  - Symbyax - A combination of olanzapine and fluoxetine used in the treatment of bipolar depression.
  - Tetrabenazine (Nitoman® in Canada and Xenazine® in New Zealand and some parts of Europe) is similar in function to antipsychotic drugs, though isn't generally considered an antipsychotic itself. This is likely due to its main usefulness being the treatment of hyperkinetic movement disorders such as Huntington's Disease and Tourette syndrome, rather than for conditions such as schizophrenia. Also, rather than having the potential to cause tardive dyskinesia that most antipsychotics have, tetrabenazine can actually be an effective treatment for the condition.

The most common antipsychotic drugs are now off-patent, meaning any pharmaceutical company is legally allowed to produce cheap generic versions of these medications. Whilst this makes them a great deal cheaper than the atypical drugs which are still being manufactured under patent constraints, atypical drugs are preferred as a first line treatment due to the fact that they are believed to have fewer side effects and seem to have additional benefits for the 'negative symptoms' of schizophrenia, a typical condition for which they might be prescribed.

Drug action and effectiveness

All antipsychotic drugs tend to block the D_2 receptors in the dopamine pathways in the brain, so the normal effect of dopamine release in the relevant synapses is reduced.

It is the blockade of D_2 receptors in the mesolimbic pathway of the brain which is thought to produce the intended antipsychotic effect.

Typical antipsychotics are not particularly selective and also block the same receptors in the mesocortical pathway, tuberoinfundibular pathway and the nigrostriatal pathway. Blocking D_2 receptors in these other pathways is thought to produce some of the unwanted side effects that the typical antipsychotics can produce (see below).

Atypical antipsychotic drugs have a similar blocking effect on D_2 receptors but seem to be a little more selective, targeting the intended pathway to a larger degree than the others. They also block or partially block serotonin receptors (particularly $5HT_{2A,C}$ and $5HT_{1A}$ receptors).

This combination of effects on both dopamine and serotonin receptors might be why atypical antipsychotic drugs tend to have fewer side effects than typicals and have a seemingly additional effect on the 'negative symptoms' of schizophrenia.

Anti-psychotics can be classified on a spectrum of low potency to high potency, where potency refers to the ability of the drug to bind to dopamine receptors, and not to the effectiveness of the drug. High potency antipsychotics such as haloperidol typically have doses of a few milligrams and cause less sleepiness and calming effects than low potency antipsychotics such as chlorpromazine, which have dosages of several hundred milligrams.

Some people who become psychotic do not seem to respond to antipsychotic medication, despite studies showing that the drug is blocking the same number of receptors as in other people who do respond to the treatment.

Side effects

The range of interactions can produce different adverse effects including extrapyramidal reactions, including acute dystonias, akathisia, parkinsonism (rigidity and tremor), tardive dyskinesia, tachycardia, hypotension, impotence, lethargy, seizures, and hyperprolactinaemia.

The atypical antipsychotics (especially olanzapine) seem to cause weight gain more commonly than the typical antipsychotics. The well documented metabolic side effects associated with weight gain include diabetes that, not infrequently, can be life threatening.

Clozapine also has a risk of inducing agranulocytosis, a potentially dangerous reduction in the number of white blood cells in the body. Because of this risk, patients prescribed

clozapine may need to have regular blood checks to catch the condition early if it does occur, so the patient is in no danger.

One of the more serious of these side effects is tardive dyskinesia, in which the sufferer may show repetitive, involuntary, purposeless movements often of the lips, face, legs or torso. (Photos and video can be seen here). It is believed that there is a greater risk of developing tardive dyskinesia with the older, typical antipsychotic drugs, although the newer antipsychotics are now also known to cause this disorder. It is believed by some that the risk of tardive dyskinesia can be reduced by combining the anti-psychotics with diphenhydramine or benztropine, though this has not been established. Central nervous system damage is also associated with irreversible tardive akathisia and/or tardive dysphrenia.

A potentially serious side effect of many antipsychotics is that they tend to lower an individuals seizure threshold. Chlorpromazine and clozapine particularly, have a relatively high seizurogenic potential. Fluphenazine, haloperidol, pimozide and risperidone exhibit a relatively low risk. Caution should be exercised in individuals that have a history of seizurogenic conditions (such as epilepsy, or brain damage).

Another serious side effect is neuroleptic malignant syndrome, in which the drugs appear to cause the temperature regulation centers to fail, resulting in a medical emergency as the patient's temperature suddenly increases to dangerous levels.

Another problematic side effect of antipsychotics is dysphoria, meaning that it just makes the patient feel bad. This side-effect is a major problem for patients with schizophrenia in that it causes them to discontinue medication, and this produces a relapse of psychotic symptoms.

Whilst this may seem a daunting list, it must be noted that many people suffer few of the obvious side effects from taking antipsychotic medication. Some side effects, such as subtle cognitive problems, foot rocking, or drooling, in the case of akinesia go unnoticed.

Other symptoms of akinesia of antipsychotics include deterioration of teeth due to a lack of saliva. These symptoms are hard to spot and are often dismissed.

Typical vs Atypical comparison

While the atypical, second-generation medications were marketed as offering greater efficacity in reducing psychotic symptoms while reducting side effects (and extra-pyramidal symptoms in particular) than typical medications, these results showing these effects often lack robustness. To remediate this problem, the NIMH conducted a recent multi-site, double-blind, study (the CATIE project), which was published in 2005. This study compared several atypical antipsychotics to an older typical antipsychotic, perphenazine, among 1493 persons with schizophrenia. Perphenazine was chosen because of its lower potency and moderate side-effect profile. The study found that only olanzapine outperformed perphenazine in the researchers' principal outcome, the discontinuation rate. The authors also noted the apparent superior efficacy of olanzapine to the other drugs for greater reduction in psychopathology, longer duration of successful treatment, and lower rate of hospitalizations for an exacerbation of schizophrenia. In contrast, no other atypical studied (risperidone, quetiapine, and ziprasidone) did better than the typical perphenazine on those measures. Olanzapine, however, was associated with relatively severe metabolic effects: subjects with

olanzapine showed a major weight gain problem and increases in glycose, cholesterol, and triglycerides. The average weight gain (1.1 kg/month, or 44 pounds for the 18 months that lasted the study) casts serious doubt on the potentiality of long-term use of this drug. Perphenazine did not create more extrapyramidal side-effect as measured by rating scales (a result supported by a meta-analysis by Dr. Leucht published in Lancet), although it should be noted that more patients discontinued perphenazine owing to extrapyramidal effects compared to the atypical agents (8 percent vs. 2 percent to 4 percent, P=0.002).

A phase 2 part of this study roughly replicated these findings. This phase consisted on a second randomization of the patients who discontinuated the taking of medication in the first phase. Olanzapine was again the only medication to stand out in the outcome measures, although the results did not always reach statistical significance, in part to the decrease of power. Perphenazine again did not create more extrapyramidal effects.

A subsequent phase was conducted. This phase innovated in allowing clinicians to offer clozapine. Clozapine indeed proved to be more effective at reducing medication drop-outs than other neuroleptic agents. Researchers also observed a trend showing clozapine with a greater reduction of symptoms. However, the potential of clozapine to cause toxic side effects, including agranulocytosis, limits the prescription to persons with schizophrenia.

History and design

The original antipsychotic drugs were happened upon largely by chance and were tested empirically for their effectiveness.

The first antipsychotic was chlorpromazine, which was developed as a surgical anesthetic. It was first used on psychiatric patients in the belief that it would have a calming effect. However, the drug soon appeared to reduce psychosis beyond this calming effect, and now some believe that it causes a reduction of psychosis unrelated to the sedating effect of the medication. It was introduced for the treatment of psychosis during the period when lobotomy was a common treatment and was hailed as a "cure" for schizophrenia. It was then touted to provide a "chemical lobotomy," causing similar neurological effects without requiring surgery.

The newer atypical antipsychotics are supposedly rationally designed drugs in which a theoretical understanding of both the condition to be treated and the effect of certain molecules on the body is used to develop potential new drug candidates.

See also

- Dopamine

Atypical antipsychotics

The *atypical antipsychotics* (also known as second generation antipsychotics) are a class of prescription medications used to treat psychiatric conditions. All atypical antipsychotics are FDA approved for use in the treatment of schizophrenia. Some carry FDA approved

indications for acute mania, bipolar mania, psychotic agitation, bipolar maintenance, and other indications.

History

The first atypical antipsychotic medication, clozapine, was discovered in the 1950s, and introduced in clinical practice in the 1970s. Clozapine fell out of popularity due to concerns over drug-induced agranulocytosis. With research indicating its effectiveness in treatment-resistant schizophrenia and the development of an adverse event monitoring system, clozapine reemerged as a viable antipsychotic. Despite the effectiveness of clozapine for treatment-resistant schizophrenia, agents with a more favorable side effect profile were sought after for widespread use. During the 1990s, olanzapine, risperidone, and quetiapine were introduced, with ziprasidone and aripiprazole following in the early 2000s.

The atypical antipsychotics have found favor among clinicians and are now considered to be first line treatments for schizophrenia and are gradually replacing the typical antipsychotics. Most researchers agree that the defining characteristic of an atypical antipsychotic is the decreased propensity of these agents to cause extrapyramidal side effects and an absence of sustained prolactin elevation.

Pharmacology of the atypicals

The mechanism of action of these agents is unknown, and likely differs to some extent among the various drugs within the class. Indeed, the receptor binding profile of the atypical antipsychotics varies quite substantiably, and this variability may be responsible for clinical differences, such as patient response and side effect profile. While modulation of the dopamine neurotransmitter system is necessary for antipsychotic activity, the role of the serotonergic activity of the atypicals is debated. Some researchers believe that D2 receptor antagonism, coupled with 5-HT2A receptor antagonism, is responsible for the "atypicality" of atypical antipsychotics. Others believe that fast dissociation (a fast Koff) from the D2 receptor, allowing for better transmission of normal physiological dopamine surges, better explains the pharmacological evidence.

There is extensive evidence that atypical antipsychotics have less of an affinity for D2 receptors and more of an affinity for the D4 receptors. This is primarily because atypical antipsychotics are somewhat less likely to cause tardive dyskinesia. The idea is that D2 receptors are dopaminergically ubiquitous and affect the motor system as much as the motivational aspect of the dopamine system. On the other hand, D4 is a more accurate dopamine receptor subtype. Atypical antipsychotics also affect the norepinephrine, acetylcholine, and histamine receptors of various subtypes.

Side effects

The side effects reportedly associated with the various atypical antipsychotics vary and are medication-specific. Generally speaking, atypical antipsychotics are associated with fewer extrapyramidal side effects and less propensity for the development of tardive dyskinesia than the typical antipsychotics. In 2004, the Committee for the Safety of Medicines (CSM) in the UK issued a warning that olanzapine and risperidone should not be given to elderly patients with dementia, because of an increased risk of stroke. Sometimes

atypical antipsychotics can cause abnormal shifts in sleep patterns, and extreme tiredness and weakness.

Tardive Dyskinesia

The main advantage to taking atypical antipsychotics over older anti-psychotics (such as Haldol) is the decreased risk of developing tardive dyskinesia. However, all of the atypical antipsychotics warn about the possiblity of tardive dyskinesia in their package inserts and in the PDR. It is not possible to truly know the risks of tardive dyskinesia when taking atypicals, because tardive dyskinesia can take many decades to develop and the atypical antipsychotics are not old enough to have been tested over a long enough period of time to determine all of the long-term risks.

Still, it is safe to say that the atypicals will probably not cause tardive dyskinesia as often as older anti-psychotics do. However, the atypicals may cause serious metabolic disorders to make them equally dangerous as the older anti-psychotic drugs.

Metabolic side effects with atypical antipsychotics

Recently, metabolic concerns have been of grave concern to clinicians, patients and the FDA. In 2003, the Food and Drug Administration (FDA) required all manufacturers of atypical antipsychotics to change their labeling to include a warning about the risks of hyperglycemia and diabetes with atypical antipsychotics. It must also be pointed out that although all atypicals must carry the warning on their labeling, some evidence shows that all atypicals are not equal in their effects of weight and insulin sensitivity. The general consensus is that clozapine and olanzapine are associated with the greatest effects on weight gain and decreased insulin sensitivity, followed by risperidone and quetiapine. Ziprasidone and aripiprazole are thought to have the smallest effects on weight and insulin resistance, but clinical experience with these newer agents is not as developed as that with the older agents.

The issue of metabolic side effects such as hyperglycemia with these medications is somewhat clouded by the fact that drug-naïve schizophrenics also appear to have an increased incidence of impaired glucose metabolism. The question is whether the increased risk for diabetes and hyperglycemia is a function of the disease state of schizophrenia, or whether these metabolic effects are the result of adverse medication side effects. It is probably an interaction involving both of these factors that is responsible for the observations of increased adverse metabolic events in patients taking atypical antipsychotics.

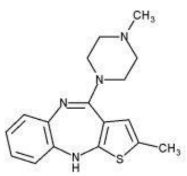
Atypical antipsychotic medications

- Clozapine (Clozaril®) (FDA-approval: 1990) Available only in oral tablets.

Risperidone (Risperdal®) (FDA-approval: 1993) Available in oral tablets, dissolving tablets, liquid form, and extended release intramusclar injection.

Olanzapine (Zyprexa®) (FDA-approval: 1996) Available in oral tablets, dissolving tablets, and intramuscular injection.
Quetiapine (Seroquel®) (FDA-approval: 1997) Available only in oral tablets.
Ziprasidone (Geodon®) (FDA-approval: 2001) Available in oral capsules and intramuscular injection.
Aripiprazole (Abilify®) (FDA)-approval: 2002) Available in oral tablets and dissolving tablets.
Sertindole (Serlect®, Serdolect®) (Not approved by the FDA for use in the USA).
Zotepine (Not approved by the FDA for use in the USA).
Amisulpride (Not approved by the FDA for use in the USA).

Olanzapine (Zyprexa)



Systematic (IUPAC) name

2-methyl-4-(4-methyl-1-piperazinyl)-
10H-thieno[2,3-b][1,5]benzodiazepine

Identifiers

CAS number 132539-06-1

ATC code N05**AH03**

PubChem 4585

DrugBank **132539-06-1**

Chemical data

Formula $C_{17}H_{20}N_{4}S$

Mol. weight 312.439

Pharmacokinetic data

Metabolism Hepatic

Half life 21-54 hours

Therapeutic considerations

Pregnancy cat. C

Legal status Prescription only

Routes oral

Olanzapine (oh-LAN-za-peen, sold as *Zyprexa*®, *Zydis*®, or in combination with fluoxetine, as *Symbyax*®) was the third atypical antipsychotic to gain approval by the Food and Drug Administration (FDA) and has become one of the most commonly used atypical antipsychotics. Olanzapine has been approved by the FDA for the treatment of schizophrenia, acute mania in bipolar disorder, agitation associated with schizophrenia and bipolar disorder, and as maintenance treatment in bipolar disorder and psychotic depression.

It has also been established in treating depression off-label because of its mood-stabilizing properties and its ability to increase the efficacy of antidepressants. Olanzapine is manufactured and marketed by the pharmaceutical company Eli Lilly and Company. It is available as a pill that comes in the strengths of 2.5 mg, 5 mg, 7.5 mg, 10 mg, 15 mg, and 20 mg and as as Zydis orally disintegrating tablets in the strengths of 5 mg, 10 mg, 15 mg, and 20 mg. It is also available as a rapid-acting intramuscular injection for short term acute use.

Case-reports, open-label, and small pilot studies suggest efficacy of olanzapine for the treatment of some anxiety spectrum disorders (e.g. general anxiety disorder, panic disorder, post-traumatic stress disorder); however, olanzapine has not been rigorously evaluated in randomized, placebo-controlled trials for this use and is not FDA approved for these indications. Other common off-label uses of olanzapine include the treatment of eating disorders (e.g. anorexia nervosa) and as an adjunctive treatment for major depressive disorder with psychotic features.

Pharmacology

Olanzapine is structurally similar to clozapine, and is classified as a thienobenzodiazepine. Olanzapine has a high affinity for dopamine and serotonin receptors. Like most atypical antipsychotics compared to the older typical ones, Olanzapine has a lower affinity for histamine, cholinergic muscarinic and alpha adrenergic receptors. The mechanism of action of olanzapine is unknown, however it is theorized that olanzapine's antipsychotic activity is mediated primarily by antagonism at dopamine receptors(does not allow dopamine to activate the dopamine receptors), specifically D2. Serotonin antagonism may also play a role in the effectiveness of olanzapine, but the significance of 5-HT2A antagonism is debated among researchers. Antagonism at muscarinic, histaminic and alpha adrenergic receptors likely explains some of the side effects of olanzapine, such as anticholinergic effects, weight gain, sedation and orthostatic hypotension.

Pharmacokinetics

Olanzapine displays linear kinetics. Its elimination half-life ranges from 21 to 54 hours. Steady state plasma concentrations are achieved in about a week. Olanzapine undergoes extensive first pass metabolism and bioavailability is not affected by food.

Metabolism

Olanzapine is metabolized by the Cytochrome P450 system isoenzymes 1A2 and 2D6 (minor pathway). Drug metabolism may be increased or decreased by agents that induce (e.g. cigarette smoke) or inhibit (e.g. fluvoxamine or ciprofloxacin) CYP1A2 activity respectively.

Adverse events

Adverse events reported in the package insert for olanzapine include dry mouth, dizziness, sedation, insomnia, orthostatic hypotension and akathisia. Olanzapine is reported to cause extrapyramidal symptoms, tardive dyskinesia and neuroleptic malignant syndrome, although at a much reduced rate when compared to the classical anti-psychotics.

Recently the FDA required the manufacturers of all atypical antipsychotics to include a warning about the risk of hyperglycemia and diabetes with atypical antipsychotics. Additionally there are some case reports of olanzapine-induced diabetic ketoacidosis. There is data showing that olanzapine can decrease insulin sensitivity. In addition, increased triglyceride levels may also be an issue with olanzapine. Impaired glucose metabolism, high triglycerides, and obesity have been shown to be constituents of the metabolic syndrome and may increase the risk of cardiovascular disease. The data suggests that olanzapine may be more likely to cause adverse metabolic effects than some of the other atypical antipsychotics.

Citing an increased risk of stroke, in 2004 the Committee for the Safety of Medicines (CSM) in the UK issued a warning that olanzapine and risperidone, both atypical antipsychotic medications, should not be given to elderly patients with dementia.

The results of a large, random-design study funded by NIH's National Institute of Mental Health (NIMH) were published in September 2005. The 18-month study, which involved 1,400 participants at 57 sites around the country, found that "patients on olanzapine also experienced substantially more weight gain and metabolic changes associated with an increased risk of diabetes than those participants taking the other drugs." [1]

Data from a small, open-label, non-randomized study seems to suggest that taking olanzapine by orally dissolving tablets may not be associated with the same degree of weight gain as conventional tablet formulations (de Haan, et al. Psychopharmacology 2004 Sep;175(3):389-90); however this has not been substantiated in a blinded experimental setting.

According to information made available from the U.S. National Library of Medicine the effects of olanzapine on children under the age of eighteen have not been thoroughly researched. Additionally, it is not clearly understood what effect, if any, olanzapine might

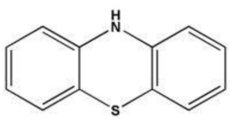
have on the unborn child of a mother who is being treated with the drug. Laboratory tests have shown that olanzapine can penetrate the placenta in animals. It is also unknown whether or not olanzapine is transferable in human breast-milk. Olanzapine does, however, pass in the breast-milk of laboratory animals.

The effects of olanzapine, in conjunction with other drugs has not been fully studied. Alcohol and any other centrally acting drugs should be avoided while taking olanzapine.

Overdose

Symptoms of an overdose include tachycardia, agitation, dysarthria, decreased consciousness and coma. Death has been reported after an acute overdose of 450mg, but also survival after an acute overdose of 1500mg.

Phenothiazines



Systematic name 10H-phenothiazine

Other names thiodiphenylamine, dibenzothiazine

Molecular formula $C_{12}H_9NS$

Molar mass 199.2762 g/mol

Appearance yellow rhombic leaflets or diamond-shaped plates

CAS number 92-84-2

Properties

Density and phase: solid at STP

Soluble benzene, ether, hot acetic acid, ethanol (slightly), mineral oil (slightly)

Insoluble water, petroleum ether, chloroform

Melting point 185 °C

Boiling point 371 °C

Acidity (pK_a) approx 23 in DMSO

Except where noted otherwise, data are given for materials in their standard state (at 25 °C, 100 kPa)

Phenothiazine (a phenol derivative of thiazine) is a pesticide and industrial chemical used in pharmaceutical manufacturing. It is sometimes used as an antihelminthic. It was introduced by DuPont as an insecticide in 1935. It is now most commonly used as an intermediate chemical in the manufacture of various psychiatric drugs.

Phenothiazine-derivative drugs

The word "phenothiazines" is used to describe the largest of the five main classes of antipsychotic drugs. Although these drugs are generally effective, there are often serious side effects including tardive dyskinesia and sedation (especially in the early stages of treatment).

There are three groups of phenothiazines, differing by their chemical structure and their pharmacological effects:

Group	Autonomic	Example	Sedative	Extrapyramidal side-effect
Aliphatic compounds	moderate	Chlorpromazine (Thorazine, Largactil)	strong	moderate
		Promazine	moderate	moderate
		Triflupromazine (Vesprin)	strong	moderate/strong
		Levomepromazine (Nozinan)	extremely strong	low
Piperidines	strong	Mesoridazine	strong	weak
		Thioridazine (Mellaril)	strong	weak
Piperazines	weak	Fluphenazine	weak/moderate	strong
		Perphenazine	weak/moderate	strong
		Prochlorperazine (Compazine, Stemetil)		
		Trifluoperazine (Stelazine)	moderate	strong

References

- ʻ History of Insecticides and Control Equipment Clemson University Pesticide Information Program.

1. ʻ Hendricks, Christensen, J.B., and Kristiansen, Jette E. Sonderborg, Denmark. "Antibakterielle Eigenschaften der Phenothiazine: Eine Behandlungsoption für die Zukunft?" Chemotherapie Journal. 13.5. (2004): 203–205. Wissenschaftliche Verlagsgesesellschaft mbH. 21 August 2005. (PDF).

Tardive dyskinesia

Tardive dyskinesia

Classifications and external resources

ICD-9

333.82

OMIM

272620

DiseasesDB

12909

eMedicine

neuro/362

Tardive dyskinesia is a serious neurological disorder caused by the long-term and/or high-dose use of dopamine antagonists, usually antipsychotics and among them especially the typical antipsychotics. These neuroleptic drugs are generally prescribed for serious psychiatric disorders. The older typical antipsychotics, which appear to cause tardive dyskinesia somewhat more often than the newer atypical antipsychotics, are being prescribed less frequently. There are some new uses, however, such as year-long implants that are being developed using the older typicals, e.g., Haldol®, one of the worst offenders when it comes to tardive dyskinesia. Other dopamine antagonists that can cause tardive dyskinesia are drugs for gastrointestinal disorders (for example metoclopramide) and neurological disorders. Some drugs that are not intended to affect dopamine, such as SSRI antidepressants, may also cause tardive dyskinesia. Newer atypical antipsychotics such as olanzapine and risperidone appear to cause tardive dyskinesia somewhat less frequently.

The term *tardive dyskinesia* was introduced in 1964. Dyskinesia means "abnormal movement" and tardive means "late", signifying that the dyskinesia only occurs after some time has elapsed following initial administration of the neuroleptic drug.

Features

Tardive dyskinesia is characterized by repetitive, involuntary, purposeless movements. Features of the disorder may include grimacing, tongue protrusion, lip smacking, puckering and pursing of the lips, and rapid eye blinking. Rapid movements of the arms, legs, and trunk may also occur. Impaired movements of the fingers may appear as though the patient is playing an invisible guitar or piano. Tardive dyskinesia, like Tourette Syndrome, can be considered an 'opposite' of Parkinson's disease. Patients with Parkinson's disease have difficulty moving, while patients with tardive dyskinesia have difficulty NOT moving.

Other closely related neurological disorders have been recognized as variants of tardive dyskinesia. Tardive akathisia involves painful feelings of inner tension and anxiety and a compulsive drive to move the body. In the extreme, the individual undergoes internal torture

and can no longer sit still. Tardive tourettism is a tic disorder that can closely mimic Tourette Syndrome, sometimes to the point where the two can only be distinguished by the details of their onsets.

Cause

The cause of tardive dyskinesia appears to be related to damage to the system that uses and processes the neurotransmitter dopamine. It is thought that postsynaptic dopaminergic receptors become supersensitive to stimulation as a result of the use of neuroleptic drugs and that this supersensitivity causes the symptoms of tardive dyskinesia. The available research seems to suggest that the concurrent prophylactic use of a neuroleptic and an antiparkinsonian drug is useless to avoid early extrapyramidal side-effects and may render the patient more sensitive to tardive dyskinesia. Since 1973 the use of these drugs have been found to be associated with the development of tardive dyskinesia (Crane, 1973). Since some of the symptoms of tardive dyskinesia can be interpreted as schizophrenia by doctors, they may prescribe additional neuroleptic drugs to treat it, leading to increased risk of more prevalent tardive dyskinesia. Several studies have indicated that long-term neuroleptic use is associated with both cognitive deterioration and atrophy of the brain (Breggin, 1990; Gualtieri and Barnhill, 1988).

Treatment

Primary prevention of tardive dyskinesia is achieved by using the lowest effective dose of a neuroleptic for the shortest time. If tardive dyskinesia is diagnosed, the causative drug should be reduced or discontinued if possible. Tardive dyskinesia may persist after withdrawal of the drug for months, years, or even permanently. There is no known cure for tardive dyskinesia, but preliminary research suggests that the atypical neuroleptic clozapine (Clozaril®) may improve the state of the patient. Improvements are also seen in some cases, if the high potency benzodiazepines - lorazepam (Ativan®), diazepam (Valium®), or clonazepam (Klonopin®)--are used. The findings about the effects of natural substances, such as vitamin E (Alpha-Tocopherol) or melatonin, are inconclusive. Treatment with adrenergic blocking agents and dopamine agonists like bromocriptine also remains somewhat controversial. There have been some reports of promising effects from the drug tetrabenazine (a different kind of neuroleptic). On the contrary, most antiparkinsonian drugs worsen the state of the patient.

Caveats

Natural remedies are unproven, since they are seldom tested in a controlled setting such as a drug trial. Preliminary research indicates that alternating rest, and regular exercise also negate the symptoms of tardive dyskinesia, necessary for all mental health outpatients who must maintain anti-psychotic neuroleptic drug regimes, for on-going 'wellness'. Switching to a newer drug with less side-effects, might be an option - in a controlled / monitored environment.

Epidemiology

Tardive dyskinesia most commonly occurs in patients with psychiatric conditions who are treated with antipsychotic medications for many years. Some estimates suggest that it occurs in 15-30% of patients receiving treatment with antipsychotic neuroleptic medications for 3 months or longer. Other estimates suggest that with each year of neuroleptic use, 5% of the patients will show signs of tardive dyskinesia, i.e., 5% after one year, 10% after two years, 15% after three years with no clear upper limit. Eventually, according to these estimates, if on the drugs long enough, the majority of patients will develop the disorder.[2] The incidence of tardive dyskinesia varies with the type of neuroleptic (e.g., haloperidol (Haldol®) more often than perphenazine (Trilafon®)), daily dose and duration of treatment (the higher the daily dose and the longer the duration of treatment, the higher the risk).

The elderly and female patients are more prone to develop tardive dyskinesia. Cigarette smokers also have a higher prevalence of tardive dyskinesia. Children and adolescents are much more sensitive to the early and late extrapyramidal side-effects of neuroleptics than adults. Because of this, treatment of youngsters with neuroleptics may be contraindicated, and many authorities believe that they should be initiated only as a last resort, using the lowest dose regime possible and the shortest duration of treatment in accordance with good patient management.

Tardive dyskinesia can become a thoroughly debilitating social handicap. Some believe the devastating impact of tardive dyskinesia illustrates why patients and/or their families (guardians and/or caregivers/nurses) should receive full information about the neuroleptic before starting treatment (informed consent).

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Typical antipsychotics

Typical antipsychotics (sometimes referred to as *conventional antipsychotics*, *classical neuroleptics* or *major tranquilizers*) are a class of antipsychotic drugs first developed in the 1950s and used to treat psychosis (in particular, schizophrenia), and are generally being replaced by atypical antipsychotic drugs. Typical antipsychotics may also be used for the treatment of acute mania, agitation, and other conditions.

Traditional antipsychotics are broken down into low-potency and high-potency classifications. Fluphenazine and haloperidol are examples of high-potency typical antipsychotics, and chlorpromazine is an example of a low potency antipsychotic. High-potency typical antipsychotics tend to be associated with more extrapyramidal side effects (EPS) and less histaminic (e.g. sedation), alpha adrenergic (e.g. orthostasis) and anticholinergic (e.g. dry mouth) side effects, while low-potency typical antipsychotics tend to be associated with less EPS but more H1, alpha1, and muscarinic side effects.

Depot injections

Some of the high-potency antipsychotics, particularly haloperidol and fluphenazine, have been formulated as the decanoate ester (e.g. fluphenazine decanoate) to allow for a slow release of the active drug when given as a deep, intramuscular injection. This has the advantage of providing reliable dosing for a person who has trouble with compliance. Depot injections can also be used for involuntary community treatment patients to ensure compliance with a community treatment order when the patient would refuse to take daily oral medication. For practical reasons, depot preparations are limited to high-potency antipsychotics so the treating physician has a limited choice. It is therefore preferable to use oral medications if the cooperation and compliance of the patient can be obtained.

Common side effects

Side effects vary among the various agents in this class of medications, but common side effects include: dry mouth, muscle stiffness, muscle cramping, tremors, EPS and weight-gain. EPS is a cluster of symptoms consisting of parkinsonism, dystonias, and akathisia. Anticholinergics such as benztropine and diphenhydramine are commonly prescribed to treat the symptoms of EPS.

Risks of serious side effects

There is a significant risk of the serious condition tardive dyskinesia developing as a side effect of typical antipsychotics. The risk of developing tardive dyskinesia after chronic typical antipsychotic usage varies on several factors, such as age and gender. The commonly reported incidence of TD among younger patients is about 5% per year. Among older patients incidence rates as high than 20% per year have been reported. The average prevalence is approximately 30%. There are no treatments that have consistently been

shown to be effective for the treatment of tardive dyskinesias, however branched chain amino acids, melatonin, and vitamin E have been suggested as possible treatments. The atypical antipsychotic clozapine has also been suggested as an alternative antipsychotic for patients experiencing tardive dyskinesia. Tardive dyskinesia may reverse upon discontinuation of the offending agent or it may be irreversible.

Neuroleptic malignant syndrome, or NMS, is a rare, but potentially fatal side effect of antipsychotic treatment. NMS is characterized by fever, muscle rigidity, autonomic dysfunction, and altered mental status. Treatment includes discontinuation of the offending agent and supportive care.

The role of typical antipsychotics has come into question recently as studies have suggested that atypical antipsychotics may increase the risk of death in elderly patients. A retrospective cohort study from the New England Journal of Medicine on Dec. 1, 2005 showed an increase in risk of death with the use of typical antipsychotics that was on par with the increase shown with atypical antipsychotics. This has led some to question the common use of antipsychotics for the treatment of agitation in the elderly, particularly with the availability of alternatives such as mood stabilizing and antiepileptic drugs.

Typical medications

- Chlorpromazine (Largactil®, Thorazine®)
Fluphenazine (Prolixin®)

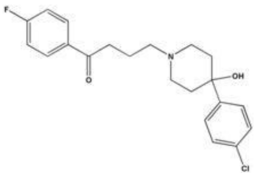
- Haloperidol **(Haldol®)**

- Molindone
Thiothixene (Navane®)
Thioridazine (Mellaril®)
Trifluoperazine
Loxapine (Loxapac®, Loxitane®)
Perphenazine
Prochlorperazine (Compazine®, Buccastem®, Stemetil®)
Pimozide (Orap®)

See also

- Atypical antipsychotics

Haloperidol



Systematic (IUPAC) name

4-[4-(4-chlorophenyl)-4-hydroxy-1-piperidyl]-1-(4-fluorophenyl)-butan-1-one

Identifiers

CAS number 52-86-8

ATC code N05**AD01**

PubChem 3559

DrugBank APRD00538

Chemical data

Formula $C_{21}H_{23}NClFO_2$

Mol. weight 375.90 (plain haloperidol)

Pharmacokinetic data

Bioavailability approx. 60 to 70% (tablets and liquid)

Metabolism hepatic

Half life 12 to 36 hours

Excretion biliar/urine

Therapeutic considerations

Pregnancy cat. C

Legal status P*rescription only*

Routes oral, IM, IV, decanoate

Haloperidol (sold under the tradenames *Aloperidin*, *Bioperidolo*, *Brotopon*, *Dozic*, *Duraperidol* (Germany), *Einalon S*, *Eukystol*, *Haldol*, *Halosten*, *Keselan*, *Linton*, *Peluces*, *Serenace*, *Serenase*, *Sigaperidol*) is a conventional butyrophenone antipsychotic drug. It was developed in 1957 by the Belgian company Janssen Pharmaceutica and submitted to first clinical trials in Belgium in the same year. After being rejected by U.S. company Searle due to side effects, it was later marketed in the U.S. by McNeil Laboratories.

Chemistry

Haloperidol is an odourless white to yellow crystalline powder. Its chemical name is 4-[4-(p-chlorophenyl)-4-hydroxypiperidino]-4'-fluorobutyrophenone and its empirical formula is $C_{21}H_{23}ClFNO_2$

Pharmacology

Haloperidol is a neuroleptic and a butyrophenone. Due to its strong central antidopaminergic action, it is classified as a highly potent neuroleptic. It is approximately 50 times more potent than chlorpromazine on a weight basis (50mg chlorpromazine are equivalent to 1mg haloperidol). Haloperidol possesses a strong activity against delusions and hallucinations, most likely due to an effective dopaminergic receptor blockage in the mesocortex and the limbic system of the brain. It blocks the dopaminergic action in the nigrostriatal pathways, which is the probable reason for the high frequency of extrapyramidal-motoric side-effects (dystonias, akathisia, pseudoparkinsonism). It has minor antihistaminic and anticholinergic properties, therefore cardiovascular and anticholinergic side-effects such as hypotension, dry mouth, constipation, etc., are seen quite infrequently, compared with less potent neuroleptics such as chlorpromazine. Haloperidol also has sedative properties and displays a strong action against psychomotor agitation, due to a specific action in the limbic system. It therefore is an effective treatment for mania and states of agitation. Additionally, it can be given as an adjuvant in the therapy of severe chronic pain.

The peripheral antidopaminergic effects of haloperidol account for its strong antiemetic activity. There, it acts at the CTZ (Chemical Trigger Zone). Haloperidol is useful to treat severe forms of nausea/emesis such as those resulting from chemotherapy. The peripheral effects lead also to a relaxation of the gastric sphincter muscle and an increased release of the hormone prolactin, with the possible emergence of breast enlargement and secretion of milk (lactation) in both sexes.

Pharmacokinetics

Oral dosing

Haloperidol is well absorbed after oral dosing. There is a first pass metabolism leading to a reduced oral bioavailability of the drug (60 to 70%). Peak plasma-levels are observed after 3 to 6 hours.

Intramuscular injections

The drug is well and rapidly absorbed and has a high bioavailability. Plasma-levels reach their maximum within 20 minutes after injection.

Intravenous injections

The bioavailability is 100% and the very rapid onset of action is seen within about ten minutes. The duration of action is 3 to 6 hours. If haloperidol is given as slow IV infusion, the onset of action is retarded, but the duration prolonged compared to IV injection.

Therapeutic concentrations

Plasma levels of 4 micrograms per liter to 20 (up to 25) micrograms per liter are required for therapeutic action. The determination of plasma levels can be used to decide about dose adjustments and to check compliance, particular in long-term patients. Plasma levels in excess of the therapeutic range may lead to a higher incidence of side-effects or even pose the risk of haloperidol intoxication.

Uses

Haloperidol is used in the control of the symptoms of:

- Acute psychosis, such as drug psychosis (LSD, amphetamines, PCP), psychosis associated with high fever or metabolic disease
- Acute and chronic schizophrenia
- Acute manic phases until the concomitantly given first-line drugs such as lithium or valproate are effective
- Hyperactivity, aggression
- Acute delirium
- Otherwise uncontrollable severe behavioral disorders in children and adolescents
- Agitation and confusion associated with cerebral sclerosis
- Adjunctive treatment of alcohol and opioid withdrawal
- Treatment of neurological disorders such as tics, Tourette syndrome, and chorea
- Treatment of severe nausea/emesis (postoperative, side-effects of radiation and cancer chemotherapy)
- Adjunctive treatment of severe chronic pain, always together with analgesics
- Therapeutic trial in personality disorders such as borderline personality disorders

Some weeks or even months of treatment may be needed before a remission of schizophrenia is evident.

In some clinics the use of atypical neuroleptics (e.g. clozapine, risperidone, olanzapine, ziprasidone) is generally preferred over haloperidol, because these drugs have an

appreciably lower incidence of extrapyramidal side-effects. Each of these drugs, however, has its own spectrum of potentially serious side-effects (e.g. agranulocytosis with clozapine, weight gain with increased risk of diabetes and of stroke). Atypical neuroleptics are also much more expensive and have recently been the subject of increasing controversy regarding their efficacy in comparison to older products and side effects.

Haloperidol is considered indispensable for treating psychiatric emergency situations. It is enrolled in the World Health Organization "List of Essential Medicines".

As is common with typical neuroleptics, haloperidol is by far more active against "positive" psychotic symptoms (delusions, hallucinations etc.) than against "negative" symptoms (social withdrawal, autism etc.). The effectiveness of haloperidol against positive symptoms has not been outperformed by newer antipsychotics.

Contraindications

Absolute

- Preexisting coma
- Severe intoxication with alcohol or other central depressant drugs
- Known allergy against haloperidol or other butyrophenones or other drug ingredients

Special caution needed

- **Preexisting** Parkinson's disease

- Patients at special risk for the development of QT-Time-Prolongation (hypokalema, concomittant use of other drugs causing the QT-Syndrome)
- Compromised liver-function (as haloperidol is metabolized and eliminated mainly by the liver, dose reductions and/or spaced intervalls may be needed)
- Haloperidol may decrease the seizure-threshold. Treat patients with epilepsy and those with risk factors for the development of seizures (alcohol withdrawal, encephalopathy) with caution. Maintain existing anticonvulsive therapy.
- Patients with hyperthyreosis; the action of haloperidol is intensified and side-effcts are more likely. Initiate an effective therapy of hyperthyreosis.
- IV injections: inject slowly to avoid hypotension or orthostatic collapse. Avoid IV injections in cardiovascular unstable patients (preexisting hypotension, shock, concomitant antihypertensive therapy, heart insufficience). Prefer in these cases moderate oral or IM doses.

Side-effects

The drug is noted for its strong early and late extrapyramidal side-effects. The risk of tardive dyskinesia is around 4% per year in younger patients, higher than with most other antipsychotic drugs. In patients over the age of 45, the percentage of those afflicted can be even higher. Other predispositive factors may be female gender, prexisting affective disorder and cerebral dysfunction.

Other side effects include dry mouth, lethargy, muscle-stiffness, muscle-cramping, restlessness, tremors, and weight-gain; side effects like these are more likely to occur when the drug is given in high doses and/or during long-term treatment. Depression, severe enough to result in suicide, is quite often seen during long-term treatment. Care should be taken to detect and treat depression early in course. Sometimes the change from haloperidol to a mildly potent neuroleptic (e.g. chlorprothixene or chlorpromazine), together with appropriate antidepressant therapy, does help. Sedative and anticholinergic side-effects occur more frequently in the elderly.

Neuroleptic malignant syndrome (NMS) is a significant possible side effect. Haloperidol and fluphenazine are the two drugs which cause NMS most often. Allergic and toxic side-effects are uncommon. Skin rash and photosensitivity both occur in less than 1% of patients.

Children and adolescents are particularly sensitive to the early and late extrapyramidal side-effects of haloperidol. It is recommended to treat pediatric patients only if clearly needed and if the psychiatric or neurologic disorder is substantial.

QT prolongation with sudden death is rarely seen. Likewise, the development of thromboembolic complications are also rare.

Haloperidol has a negative impact on vigilance and decreases the ability of the patient to drive or operate a machine, particularly initially.

Abuse and dependence

Haloperidol is completely devoid of any potential psychological dependence.

Unpleasant withdrawal symptoms, if haloperidol is stopped abruptly after long-term treatment, are commonly noted. These are usually agitation, anxiety, insomnia, and nausea. Rebound of psychotic symptoms and mood swing into mania are also seen. These symptoms are not indicative of dependence. Instead of terminating treatment with haloperidol abruptly, decrease its dose, if possible, by 20 to 25% weekly. If haloperidol has to be stopped at once for medical reasons, give tranquilizers like Diazepam or Alprazolam for a few weeks, as needed, for effective alleviation of withdrawal symptoms.

Other Remarks

During long-term treatment of chronic psychiatric disorders, it should be tried - in regular intervals - to reduce the daily dose to the lowest level needed for maintenance of remission. Sometimes, it may be indicated to terminate haloperidol treatment gradually.

Other forms of therapy (psychotherapy, occupational therapy/ergotherapie, social rehabilitation) should be instituted properly.

Pregnancy and lactation

Data from animal experiments indicate haloperidol is not teratogenic, but is embryotoxic in high doses. In humans, no controlled studies exist. Unconfirmed studies in pregnant women revealed possible damage to the fetus, although most of the women were exposed to multiple drugs during pregnancy. Following accepted general principles, haloperidol should only be given during pregnancy if the benefit to the mother clearly outweighs the potential fetal risk.

Haloperidol, when given to lactating women, is found in significant amounts in their milk. Breastfed children sometimes show extrapyramidal symptoms. If the use of haloperidol during lactation seems indicated, the benefit for the mother should clearly outweigh the risk for the child. Consider termination of breastfeeding.

Carcinogenicity

So far, no statistically acceptable evidence is found to associate long-term use of haloperidol with the potential for increased breast cancer risk in female patients. In an unconfirmed study, relative risks of breast cancer, in inmates of the Buffalo Psychiatric Center undergoing long-term treatment with haloperidol, were 3.5 (compared to patients hospitalized in general or internal medicine facilities) and 9.5 (general population), respectively (authors: U. Halbreich et al, loc. cit.: 'American Journal of Psychiatry', 1996). These results need confirmation by larger studies. If true, carcinogenity is most probably related to the strong increase in plasma-levels of prolactin under long-term treatment with haloperidol. This news is another good reason to avoid any unnecessary use of haloperidol.

Interactions

- Other cental depressants (alcohol, tranquilizers, narcotics): actions and side-effects of these drugs (sedation, respiratory depression) are increased. In particular, the doses of concomitantly used opioids for chronic pain can be reduced by 50%.

Methyldopa: increased risk of extrapyramidal side-effects and other unwanted central effects

Levodopa: decreased action of levodopa

Tricyclic antidepressants: metabolism and elimination of tricyclics significantly decreased, increased toxicity noted (anticholinergic and cardiovascular side-effcts, lowering of seizure-threshold)

Quinidine, buspirone, and fluoxetine: increased plasma-levels of haloperidol, decrease haloperidol dose, if necessary

Carbamazepine, phenobarbital, and rifampicin: plasma-levels of haloperidol significantly decreased, increase haloperidol dose, if necessary.

lithium: rare cases of the following symptoms have been noted: encephalopathy, early and late extrapyramidal side-effects, other neurologic symptoms and coma. Check lithium plasma levels regularly and keep the dose of haloperidol as low as possible.

Guanethidine: antihypertensive action antagonized

Epinephrine: action antagonized, paradoxical decrease in blood pressure may result

Doses

As directed by the physician, depends on the condition to be treated, age and weight of patient:

- Acute problems: single doses of 1 mg to 5 mg (up to 10mg) oral or i.m, usually repeated every 4 to 8 hours. Do not exceed an oral dose of 100 mg daily. Doses used for IV injection are usually 5 to 10 mg as a single dose; not exceeding 50 mg daily.
- Chronic conditions: 0.5 to 20 mg daily oral, rarely more. The lowest dose that maintains remission should by employeed.
- Experimental doses: In resistant cases of psychosis small studies with oral doses of up to 300 mg daily have been conducted (in most cases together with an anticholinergic antiparkinsonian drug (Biperiden, Benzatropine etc.) to avoid severe early extrapyramidal side-effects. These studies showed no superior results and led to severe side-effcts, also the frequency of otherwise unusual side-effects (hypotension, QT-time prolongation, and serious cardiac arrhythmias) was dramatically increased. The clinical use of haloperidol in these doses is discouraged now and it is recommended to switch the patient gradually to a different neuroleptic (e.g. clozapine, olanzapine, aripiprazole).

Depot forms are also available, these are injected deeply i.m. at regular intervalls. The depot forms are not suitable for initial treatment.

Overdose

Experimental evidence from animal studies indicates that doses needed for acute poisoning are quite high in relation to therapeutic doses.

Symptoms are usually due to exaggerated side-effects. Most often encountered are:

- Severe extrapyramidal side-effects with muscle rigidity and tremors, akathisia etc. (inject 5 mg biperiden (Akineton®) slowly IV, repeat after some hours if necessary). Sometimes oral or IM treatment with biperiden is needed for several days or even weeks. If the patient is very upset about extrapyramidal side-effects, small doses of lorazepam (0.5 to 1 mg orally, repeated every 4 to 6 hours if necessary) can be given. Lorazepam has an intrinsic action against upset, anxiety, and extrapyramidal side-effects.
- Hypotension or hypertension
- Sedation
- Anticholinergic side-effects (dry mouth, constipation, paralytic ileus, difficulties in urinating, massive sweating). Cautious doses of physostigmine may be given repeatedly. *N.B. Physostigmine may increase the risk of seizures!*
- Coma in severe cases, accompanied by respiratory depression and massive hypotension, shock

- Rarely serious ventricular arrhythmia (torsades de pointes) with or without prolonged QT-time
- Epileptic seizures, give careful doses of diazepam 5 mg to 10 mg by slow IV injection, repeatedly if needed, until seizures subside. Take care not to worsen central depression or respiratory depression caused by haloperidol. The treatment facility should be able to institute artificial respiration readily. Valproate first given as slow IV infusion and later orally may also be effective.

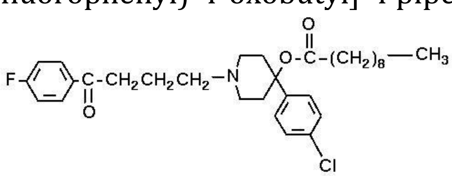
Treatment is merely symptomatic and involves intensive care with stabilization of vital functions. In early detected cases of oral overdose induction of emesis, gastric lavage and the use of activated charcoal can all be tried. Avoid epinephrine for treatment of hypotension and shock, because its action might be reversed.

Generally, the prognosis of overdose is good and lasting damage is not known, provided that the patient has survived the initial phase.

Overdoses with depot injections are uncommon, because almost always experienced personnel administer them to patients.

Other formulations

As well as haloperidol, the decanoate ester haloperidol decanoate (*Haldol decanoate*®, *Halomonth*®, *Neoperidole*®) can be used or haloperidol Lactate. The decanoate has a greatly extended duration of effect and its structural formula is 4-(4-chlorophenyl)-1-1[4-(4-fluorophenyl)-4-oxobutyl]-4 piperidinyl decanoate (see image below).



Veterinary use

Haloperidol is also used on many different kinds of animals. It appears to be particularly successful when given to birds; e.g. a parrot that will not otherwise stop plucking its feathers out.

Dose forms

- Liquid: 2 mg/mL, also 10 mg/mL
- Tablets: 0,5 mg, 1 mg, 2 mg, 5 mg, 10 mg, 20 mg
- Injection: 5 mg (1 mL)
- Depot injection forms
- The original drug Haldol® and many generics are available

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Lithium pharmacology

Lithium in pharmacology refers to the lithium ion, Li+, used as a drug. Lithium is administered in a number of chemical salts of lithium, which are used primarily in the treatment of bipolar disorder as mood stabilizing drugs. They are also sometimes used to treat depression and mania. Lithium carbonate (Li_2CO_3), sold as Carbolith®, Cibalith-S®, Duralith®, Eskalith®, Lithane®, Lithizine®, Lithobid®, Lithonate®, Lithotabs® and Maniprex®, is the most commonly prescribed, whilst the citrate salt lithium citrate ($Li_3C_6H_5O_7$), the sulfate salt lithium sulfate (Li_2SO_4), aspartate and the orotate salt lithium orotate are alternatives.

Lithium is widely distributed in the central nervous system and interacts with a number of neurotransmitters and receptors, decreasing noradrenaline release and increasing serotonin synthesis.

History

Solutions of lithium will dissolve uric acid crystals. Against the background of nineteenth century theories linking excess uric acid to a range of disorders, including manic disorders, Carl Lange in Denmark and William Hammond in New York used lithium to treat mania from the 1870s onwards.

However, by the turn of the century, the use of lithium in this way died out and was seemingly forgotten. The use of lithium salts to treat mania was rediscovered by the Australian psychiatrist John Cade in 1949, after he discovered the effect of first lithium urate, and then other lithium salts, on animals. Cade had actually been trying to test the effects of urate as a control for chemicals in urine, and used the lithium salt because it was the most soluble; the animals were tranquilized and Cade eventually tracked the effect down to the lithium itself. Cade proposed lithium as a tranquilizer, and soon succeeded in controlling mania in chronically hospitalized patients. This was one of the first successful applications of a drug to treat mental illness (perhaps the first, if herbal-source drugs like Rauwolfia are discounted), and it opened the door for the development of medicines for other mental problems in the next decades.

The rest of the world was slow to adopt this revolutionary treatment, largely because of deaths which resulted from even relatively minor overdosing, and from use of lithium chloride as a substitute for table salt. Largely through the research and other efforts of Denmark's Mogens Schou in Europe, and Samuel Gershon in the U.S., this resistance was

slowly overcome. The application of lithium for manic illness was approved by the United States Food and Drug Administration in 1970.

Treatment

Lithium treatment is used to treat mania in bipolar disorder. Initially, lithium is often used in conjunction with antipsychotic drugs as it can take up to a week for lithium to have an effect. Lithium is also used as prophylaxis for depression and mania in bipolar disorder. Also, it is sometimes used for other disorders, like cycloid psychosis, unipolar depression, migraine and others. It is sometimes used as an "augmenting" agent, to increase the benefits of standard drugs used for unipolar depression. Lithium treatment was previously considered to be unsuitable for children, however more recent studies show its effectiveness for treatment of early-onset bipolar disorder in children as young as four.

Mechanism of Action

The precise mechanism of action of Li+ as a mood-stabilizing agent is currently unknown. It is possible that Li+ produces its effects by interacting with the transport of monovalent or divalent cations in neurons. However, because it is a poor substrate at the sodium pump, it cannot maintain a membrane potential and only sustains a small gradient across biological membranes. Yet Li+ is similar enough to Na+ in that under experimental conditions, Li+ can replace Na+ for production of a single action potential in neurons.

Recent research suggests three different mechanisms which may act together to deliver the mood-stabilizing effect of this ion (Jope RS, Mol Psychiatry 1999 Mar; 4(2):117-28). An increasing number of scientists have come to the conclusion that the excitatory neurotransmitter glutamate is the key factor in understanding how lithium works. Other mood stabilizers such as valproate and lamotrigine exert influence over glutamate, suggesting a possible biological explanation for mania. The other mechanisms by which lithium might help to regulate mood include the alteration of gene expression and the non-competitive inhibition of an enzyme called inositol monophosphatase.

Unlike other psychoactive drugs, Li+ produces no obvious psychotropic effects, (such as euphoria) in normal individuals at therapeutic concentrations.

Dr. Klein and his colleagues' at the University of Pennsylvania discovered in 1996 that lithium ion deactivates the GSK-3B enzyme [1]. The regulation of GSK-3B by lithium may affect the circadian clock -- and recent research (Feb 2006) seems to concur with this conclusion. When the GSK-3B is activated, the protein Bmal1 is unable to reset the "master clock" inside the brain which disrupts the body's natural cycle. When the cycle is disrupted, the routine schedules of many functions (metabolism, sleep, body temperature) are disturbed. Lithium may thus restore disruption of a normal brain function in some people. Its complete mechanism in treatment of mood disorders remains a mystery.

Lithium toxicity and side effects

The required dosage (15-20mg per kg of body weight) is slightly less than the toxic level, requiring blood levels of lithium to be monitored extremely closely during treatment. In

order to prescribe the correct dosage, the patient's entire medical history, both physical and psychological, is taken into consideration. Blood tests are carried out every 3 months to ensure the level of lithium is appropriate and to prevent toxicity, along with kidney and thyroid tests.

Those who use lithium should receive regular (generally monthly once stable) blood tests and should monitor thyroid function annually and kidney function every three to six months for abnormalities. As it interferes with the regulation of sodium and water levels in the body, lithium can cause dehydration. Dehydration, which is compounded by heat, can result in increasing lithium levels.

High doses of haloperidol, fluphenazine, or flupenthixol may be hazardous when used with lithium; irreversible toxic encephalopathy has been reported.

Lithium salts, with the possible exception of lithium orotate, have a narrow therapeutic/toxic ratio and should therefore not be prescribed unless facilities for monitoring plasma concentrations are available. Patients should be carefully selected. Doses are adjusted to achieve plasma concentrations of 0.6 to 1.2mmol Li+/litre (lower end of the range for maintenance therapy and elderly patients, higher end for pediatric patients) on samples taken 12 hours after the preceding dose. Overdosage, usually with plasma concentrations over 1.5mmol Li+/litre, may be fatal and toxic effects include tremor, ataxia, dysarthria, nystagmus, renal impairment, and convulsions. If these potentially hazardous signs occur, treatment should be stopped, plasma lithium concentrations redetermined, and steps taken to reverse lithium toxicity.

Lithium toxicity is compounded by sodium depletion. Concurrent use of diuretics that inhibit the uptake of sodium by the distal tubule (e.g. thiazides) is hazardous and should be avoided. In mild cases withdrawal of lithium and administration of generous amounts of sodium and fluid will reverse the toxicity. Plasma concentrations in excess of 2.5 mmol Li±/litre are usually associated with serious toxicity requiring emergency treatment. When toxic concentrations are reached there may be a delay of 1 or 2 days before maximum toxicity occurs.

In long-term use, therapeutic concentrations of lithium have been thought to cause histological and functional changes in the kidney. The significance of such changes is not clear but is of sufficient concern to discourage long-term use of lithium unless it is definitely indicated. An important consequence is the development of diabetes insipidus (inability to concentrate urine). Patients should therefore be maintained on lithium treatment after 3-5 years only if, on assessment, benefit persists. Conventional and sustained-release tablets are available. Preparations vary widely in bioavailability, and a change in the formulation used requires the same precautions as initiation of treatment. There are few reasons to prefer any one simple salt of lithium; the carbonate has been the more widely used, but the citrate is also available.

Lithium teratogenicity

Though less teratogenic than initially thought, Lithium increases the risk of congenital cardiac abnormalities to ~2% of newborns.

Lithium overdose

Signs that lithium levels within the body are too high include: confusion, diarrhea, lethargy, severe tremors, and/or an upset stomach.

Lithium and culture

As with many other drugs, songs have been written about its effects, "Lithium Sunset" by Sting, "Lithium" by Nirvana, and "Lithium" by Evanescence among others.

The soft drink 7 Up, originally named "Bib-Label Lithiated Lemon-Lime Soda", contained lithium citrate until it was reformulated in 1950.

Hundreds of other soft drinks also included lithium salts or lithia waters as well as at least one brewery which produced Lithia beers (all of these were forced to remove lithium in 1948).

An early version of Coca Cola available in pharmacies' soda fountains called Lithia Coke was a mixture of Coca Cola syrup and lithia water -- lithia waters are naturally occurring mineral waters with higher lithium amounts.

The amount of lithium in any of the commercially available soft drinks was hundreds of times less than a minimum psychiatric dose but the ban didn't make any distinctions on that basis.

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Antitussives

A *cough medicine* is a drug used to treat coughing and related conditions. Dry coughs are treated with *cough suppressants* (*antitussives*) that suppress the body's urge to cough, while productive coughs (coughs that produce phlegm) are treated with expectorants that loosen mucus from the respiratory tract. These medicines are widely available in the form of cough syrup, also known as linctus.

Cough suppressants

Cough suppressants may act centrally (on the brain, and specifically the vagus nerve) or locally (on the respiratory tract) to suppress the cough reflex.

Centrally acting suppressants include dextromethorphan (DXM), noscapine, ethyl morphine and codeine.

Peripherally acting substances include local anaesthetics, which reduce the sensation of nerves in the throat, and demulcents, which coat the esophagus. Although it is commonly believed that cough medicines must coat the throat to be effective, there is no evidence that it is possible to control coughing by this means.

One might think it unwise to suppress the cough reflex (the mechanism for expelling mucus from the respiratory tract) but severe coughing may lead to lung irritation, causing a vicious cycle. The cough reflex is also very strong and cannot be completely suppressed. However, dry cough (without mucus production) or cough that is exhausting and preventing sleep should be treated with suppressants.

Recent studies have found that theobromine, a compound found in cocoa, is more effective as a cough suppressant than prescription codeine. This molecule suppresses the "itch" signal from the nerve in the back of the throat that causes the cough reflex. It is possible to get an effective dose from 50g of dark chocolate, which contains 2 to 10 times more cocoa than milk chocolate. Theobromine was also free from side effects in the blind tests.[1]

Expectorants

An expectorant (from Latin ex- "out" + pectoris "of the chest") is a medicine or herb which increases the expulsion of tracheal or bronchial mucus through expectoration or coughing. In over-the-counter preparations, guaifenesin is often used. The effectiveness of expectorants in cough medicines has been questioned; however, water is an effective expectorant and drinking adequate water thins the mucus and enables it to be expelled more easily.[1]

Herbal remedies considered to be expectorants include the following:

- Aniseed (Pimpinella anisum),

Balm of Gilead (Populus gileadensis),
Balsam of Peru (Myroxylon perierae),
Balsam of Tolu (Myroxylon toluifera),
Bloodroot (Sanguinaria canadensis),
Cannabis (Cannabis Sativa),

Cardamom (Elettaria caradamomum),
Coltsfoot (Tussilago farfara),
Comfrey (Symphytum officinale),
Elderflower (Sambucus nigra),
Elecampane (Inula helenium),
Garlic (Allium sativum),
Golden seal (Hydrastis canadensis),
Grindelia (Grindelia camporum),
Hyssop (Hyssopus officinalis),
Iceland moss (Cetraria islandica),
Irish moss (Chondrus crispus),
Liquorice (Glycyrrhiza glabra),
Lobelia (Lobelia inflata),
Lungwort (Sticta pulmonaria),
Marshmallow (Althaea officinalis),
Mouse ear (Hieracium pilosella),
Mullein (Verbascum thapsus),
Pleurisy root (Asclepias tuberosa),
Senega (Polygala senega),
Skunk Cabbage (Symplocarpus foetidus),
Squill (Urginea maritima),
Thuja (Thuja occidentalis),
Thyme (Thymus vulgaris),
Vervain (Verbena officinalis),
White horehound (Marrubium vulgare),
Wild cherry (Prunus serotona).

Cough drops

Cough drops or *throat lozenges* are tablets which people can suck to soothe the throat or to alleviate excessive coughing. They are usually small, sweetened (often with artificial sweeteners), and contain an oral anesthetic, such as menthol, which anesthesizes the receptors in the throat that cause the cough reflex. The occasional use of "lozenge" (first used in 1530, according to the Oxford English Dictionary) is due to the original lozenge shape of cough drops. Popular brands of cough drops include Fisherman's Friend, Halls, Ricola, and Luden's.

Controversy

In 2002, researchers at the University of Bristol (Schroeder & Fahey) published a study in the British Medical Journal indicating that some cough medicines are no more effective than placebos.[2] In 2006, the American College of Chest Physicians published a guideline that had the dual message that many over-the-counter cough medicines are not effective and that those that are effective in treating the symptom do not treat the underlying cause; the underlying disorder emphasized by the guideline was pertussis (whooping cough) in the

elderly.[3] This guideline has been referred to by many news articles in the lay press, which emphasize the economic impact of discouraging cough medicine use while not touching on the health concerns expressed.[4]

Many cough mixtures contain both an expectorant and a suppressant -- even though an expectorant requires the action of a cough to expel mucus. Many believe this supports the idea that cough suppression is just a placebo effect. However, in practice the two active ingredients combine to provide less coughing, but more productive coughs.

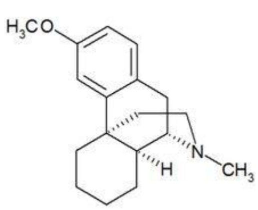
Colloquial term usage

"Cough medicine", for example "Grandpa's old cough medicine", is also a commonly used euphemism for whiskey and other strong alcoholic beverages, or even actual cough medicine such as NyQuil which in some formulations has a high alcohol content.

Notes

1. ^ **Vince, Gaia.** **"**Persistent coughs melt away with chocolate**",** *New Scientist***,** **November 22, 2004.**
2. ^ **Knut Schroeder and Tom Fahey (2002). "**Systematic review of randomised controlled trials of over the counter cough medicines for acute cough in adults**". British Medical Journal** ***324*****: 329–331.** PMID 11834560**.**
3. ^ *American College of Chest Physicians (January 9, 2006).* New Cough Guidelines Urge Adult Whooping Cough Vaccine; Many OTC Medications Not Recommended for Cough Treatment*. Press release.*
4. ^ Tanner, Lindsey. "U.S. doctors say cough syrups don't work", The News Journal from Associated Press (link is to MSNBC on-line version), January 10, 2006, pp. A3.

Dextromethorphan



Identifiers

CAS number 125-71-3

ATC code R05**DA09**

PubChem 5360696

DrugBank APRD00655

Chemical data

Formula C18H25NO

Mol. weight 271.4 g/mol

Pharmacokinetic data

Metabolism Hepatic (CYP2D6, CYP3A4 and CYP3A5-mediated)

Half life 1.4–3.9 hours

Excretion Renal

Therapeutic considerations

Pregnancy cat. $A_{(AU)}$ $C_{(US)}$

Legal status $S2_{(AU)}$

Routes Oral

Dextromethorphan (*DM* or *DXM*) is an antitussive drug that is found in many over-the-counter cold and cough preparations, usually in the form of dextromethorphan hydrobromide. It is also used as a recreational drug.

Chemistry

Dextromethorphan is a salt of the methyl ether dextrorotatory isomer of levorphanol, a narcotic (opioid) analgesic (and DXM itself is an enantiomeric isomer, that is, a mirror image in the 3D space, of levomethorphan, a substance considered an opioid[1]). It is chemically named as 3-methoxy-17-methyl-9(alpha), 13(alpha), 14(alpha)-morphinan hydrobromide monohydrate. DXM occurs as white crystals, is sparingly soluble in water, and freely soluble in alcohol. The drug is dextrorotatory in water (at 20 degrees Celsius, Sodium D-line) with a specific rotation of +27.6 degrees.

Indications

The FDA approved dextromethorphan for over-the-counter sale as a cough suppressant in 1958. This filled the need for a cough suppressant lacking the abuse liability and addictive properties of codeine phosphate, the most widely used cough medication at the time. The advantage of dextromethorphan preparations over those containing codeine (now prescription only in the United States) was the lack of physical addiction potential and

sedative side-effects, although as with most cough supressants, studies show that its effectiveness is highly debatable. See also: Cough medicine controversy

Pharmacodynamics

At therapeutic doses, the drug acts centrally to elevate the threshold for coughing, without inhibiting ciliary activity. Dextromethorphan is rapidly absorbed from the gastrointestinal tract, and exerts its activity within 15 to 60 minutes of ingestion. The duration of action after oral administration is approximately three to eight hours. Because administration of DXM can be accompanied by histamine release, its use in atopic children is very limited.

The average dosage necessary for effective antitussive therapy is between 10mg and 30mg every four to six hours.

According to the WHO committee on Drug Dependence, dextromethorphan, when used recreationally (see non-medical use of dextromethorphan), does not produce physical addiction but can generate slight psychological dependence in some users.

Clinical pharmacology

Following oral administration, dextromethorphan is rapidly absorbed from the gastrointestinal tract, where it enters the bloodstream and crosses the blood-brain barrier. The first-pass through the hepatic portal vein results in some of the drug being metabolized into an active metabolite of dextromethorphan, dextrorphan, the 3-hydroxy derivative of dextromethorphan. The therapeutic activity of dextromethorphan is believed to be caused by both the drug and this metabolite. Dextromethorphan is metabolized by various liver enzymes and subsequently undergoes O-demethylation (producing dextrorphan), N-demethylation, and partial conjugation with glucuronic acid and sulfate ions. Hours after dextromethorphan therapy, (in humans) the metabolites (+)-3-hydroxy-N-methylmorphinan, (+)-3-morphinan, and traces of the unchanged drug are detectable in the urine.

One well known metabolic catalyst involved is a specific cytochrome P450 enzyme known as 2D6, or CYP2D6. A significant portion of the population has a functional deficiency in this enzyme (and are known as poor CYP2D6 metabolizers). As CYP2D6 is the primary metabolic pathway in the inactivation of dextromethorphan, the duration of action and effects of dextromethorphan are significantly increased in such poor metabolizers. Deaths and hospitalizations have been reported in recreational use by poor CYP2D6 metabolizers.

A large number of medications (including antidepressants) are potent inhibitors of CYP2D6 (see CYP2D6 article). There exists, therefore, the potential of drug-drug interactions between dextromethorphan and concomitant medications. There have been reports of fatal consequences arising from such interactions.[2]

Dextromethorphan crosses the blood-brain barrier, and the following pharmacological actions have been reported:

- NMDA glutamatergic receptor antagonist
- Dopamine reuptake inhibitor**[3]**
- Ã1 and Ã2 receptor agonist (Zhou & Musacchio, 1991)

- ±3^{2}4 nicotinic receptor antagonist[4]
- Serotonin reuptake inhibitor[5]

History

Dextromethorphan was first patented with U.S. Patent 2,676,177, and was approved for over-the-counter purchase as an antitussive in 1958.

During the 1960s and 1970s, DXM became available in an over-the-counter tablet form by the brand name Romilar. It was put on the shelves in hopes of cutting down on codeine cough remedies. In 1973, Romilar was taken off the shelves after a burst in sales due to common recreational use. It was then replaced by cough syrup, in an attempt to cut down on recreational usage.

Fibromyalgia treatment

Dextromethorphan is currently being investigated as a potential treatment for fibromyalgia symptoms.

Recreational use

Since their introduction, preparations containing the over-the-counter drug dextromethorphan have been used in a manner inconsistent with their labeling, often as a recreational drug or to induce intoxication (sometimes referred to as "robo-tripping"). Dextromethorphan has little to no psychological effect in the doses used medically, however alteration of consciousness generally occurs following ingestion of approximately 7 to 50 times the therapeutic dose over a relatively short period of time. [2]

People who study the specific effects of psychotropic substances classify DXM as a dissociative drug, a major subclass of hallucinogenic drugs, along with Ketamine and Phencyclidine. It generally does not produce withdrawal symptoms characteristic of physically addictive substances, but psychological addiction has been reported by some users.

DXM, when consumed in low recreational doses (usually under 200mg), is often described as having a buoyant, vaguely psychedelic effect similar to a mixture of alcohol, opiates, and marijuana. With higher doses, intense euphoria and vivid imagination may occur as bizarre feelings of dissociation increase. With very high doses, profound alterations in consciousness have been noted, and users often report out of body experiences or temporary psychosis. One of the unique features of a high dose DXM trip is the ability to relive past memories. Most users find such high doses to be extremely uncomfortable and most are unwilling to repeat it. Flanging (speeding up or slowing down) of sensory input also occurs, which is another unique feature of high dose DXM trips. In 1981, a paper by Gosselin estimated the lethal dose between 50 and 500 mg/kg.

Individual reactions to recreational doses of Dextromethorphan vary widely. Some find the effects of the drug to be immensely pleasurable, similar to a combination of opiates and hallucinogens, while others find that the drug produces dysphoria, panic, or dread.

Physical side effects that can occur after ingestion of recreational doses of DXM include a blotchy skin rash, itching (sometimes referred to as "robo itch," short for "Robitussin itch"), and sweating. Many people vomit from recreational doses or feel ill for the first part of the "trip". When taken in higher doses, physical side effects can include dilated pupils, difficulty urinating, increased urination frequency, extreme diarrhea, fever, tachycardia, loss of appetite, shakiness, seizures, and possible coma and death (however, in pure DXM, this has only been reported when doses exceed 2,000 mg).

See also

- Dissociatives
    - PCP
    - Ketamine
    - Nitrous oxide
- Psychoactive drug

Footnotes

1. ^ Shulgin, Alexander (2003). DXM (Dextromethorphan). Ask Dr. Shulgin Online. Retrieved on 2006-05-31.
2. ^ a b Jones K, Taranto M (2006). "Illicit Drug Manual: Dextromethorphan ("Robo-tripping")". collegehealth-e *1* (4): 13-17.

Cannabinoids

Cannabinoids are a group of chemicals which activate the body's cannabinoid receptors. Before other types were discovered, the term referred to a unique group of secondary metabolites found in the cannabis plant, which are responsible for the plant's peculiar pharmacological effects. Currently, there are three general types of cannabinoids: herbal cannabinoids occur uniquely in the cannabis plant; endogenous cannabinoids are produced in the bodies of humans and other animals; and synthetic cannabinoids are similar compounds produced in a laboratory.

Cannabinoid receptors

Before the 1980s, it was often speculated that cannabinoids produced their physiological and behavioral effects via nonspecific interaction with cell membranes, instead of interacting with specific membrane-bound receptors. The discovery of the first cannabinoid receptors in the 1980s helped to resolve this debate. These receptors are common in animals, and have been found in mammals, birds, fish, and reptiles. There are currently two known types of cannabinoid receptors, termed CB1 and CB2.

CB1 receptors are found primarily in the brain, specifically in the basal ganglia and in the limbic system, including the hippocampus. They are also found in the cerebellum and in both male and female reproductive systems. CB1 receptors are essentially absent in the medulla oblongata, the part of the brain stem that is responsible for respiratory and cardiovascular functions. Thus, there is not a risk of respiratory or cardiovascular failure as there is with many other drugs. CB1 receptors appear to be responsible for the euphoric and anticonvulsive effects of cannabis.

CB2 receptors are almost exclusively found in the immune system, with the greatest density in the spleen. CB2 receptors appear to be responsible for the anti-inflammatory and possibly other therapeutic effects of cannabis.

Natural cannabinoids

Type

- Cannabigerol-type *CBG*
- Cannabichromene-type *CBC*
- Cannabidiol-type *CBD*
- Tetrahydrocannabinol-and Cannabinol-type *THC, CBN*
- Cannabielsoin-type *CBE*
- iso-Tetrahydrocannabinol-type *iso-THC*
- Cannabicyclol-type *CBL*
- Cannabicitran-type *CBT*

Natural cannabinoids, also called herbal cannabinoids and classical cannabinoids, are nearly insoluble in water but soluble in lipids, alcohols, and other non-polar organic solvents.

However, as phenols they form more water-soluble phenolate salts under strongly alkaline conditions. All natural cannabinoids are derived from their respective 2-carboxylic acids (2-COOH) by decarboxylation; that is, catalyzed by heat, light, or alkaline conditions. Natural cannabinoids are only known to occur naturally in the cannabis plant, and are concentrated in a viscous resin that is produced in glandular structures known as trichomes. In addition to cannabinoids, the resin is rich in terpenes, which are largely responsible for the odor of the cannabis plant.

There are over sixty known herbal cannabinoids. To the right the main classes of natural cannabinoids are shown. All classes derive from cannabigerol-type compounds and differ mainly in the way this precursor is cyclized.

Tetrahydrocannabinol (THC), cannabidiol (CBD) and cannabinol (CBN) are the most prevalent natural cannabinoids and have received the most study. Other common ones are listed below:

- CBG Cannabigerol

CBC Cannabichromene
CBL Cannabicyclol
CBV Cannabivarol
THCV Tetrahydrocannabivarin
CBDV Cannabidivarin
CBCV Cannabichromevarin
CBGV Cannabigerovarin
CBGM Cannabigerol Monoethyl Ether

THC is the primary psychoactive component of the plant. Medically, it appears to ease moderate pain and to be neuroprotective. THC has approximately equal affinity for the CB1 and CB2 receptors (Huffman 2000). Its effects are perceived to be more cerebral.

CBD is not psychoactive, and appears to moderate the euphoric effects of THC. It may decrease the rate of THC clearance from the body, perhaps by interfering with the metabolism of THC in the liver. Medically, it appears to relieve convulsion, inflammation, anxiety, and nausea. CBD has a greater affinity for the CB2 receptor than for the CB1 receptor. It is perceived to have more effect on the body.

CBN is the primary product of THC degradation, and there is usually little of it in a fresh plant. CBN content increases as THC degrades in storage, and with exposure to light and air. It is only mildly psychoactive, and is perceived to be sedative or stupefying.

These compounds may be in different forms depending on the position of the double bond in the alicyclic carbon ring. There is potential for confusion because there are different numbering systems used to describe the position of this double bond. Under the dibenzopyran numbering system widely used today, the major form of THC is called delta-9-THC, while the minor form is called delta-8-THC. Under the alternate terpene numbering system, these same compounds are called delta-1-THC and delta-6-THC, respectively.

Most herbal cannabinoid compounds are 21 carbon compounds. However, some do not follow this rule, primarily because of variation in the length of the side chain attached to the aromatic ring. In THC, CBD, and CBN, this side chain is a pentyl (5 carbon) chain. In the most common homologue, the pentyl chain is replaced with a propyl (3 carbon) chain. Cannabinoids with the propyl side chain are named using the suffix "varin", and are

designated, for example, THCV, CBDV, or CBNV. It appears that shorter chains increase the intensity and decrease the duration of the activity of the chemicals.

Cannabinoids were first discovered in the 1940s, when CBD and CBN were identified. The structure of THC was first determined in 1964. Due to molecular similarity and ease of synthetic conversion, it was originally believed that CBD was a natural precursor to THC. However, it is now known that CBD and THC are produced independently in the cannabis plant. Cannabinoid production starts when an enzyme causes geranyl pyrophosphate and olivetolic acid to combine and form CBG. Next, CBG is independently converted to either CBD or CBC by two separate synthase enzymes. CBC is then enzymatically cyclized to THC. For the propyl homologues (THCV, CBDV and CBNV), there is a similar pathway that is based on CBGV.

Cannabis plants can exhibit wide variation in the quantity and type of cannabinoids they produce. The mixture of cannabinoids produced by a plant is known as the plant's cannabinoid profile. Selective breeding has been used to control the genetics of plants and modify the cannabinoid profile. For example, strains which are used as fiber (commonly called hemp), are bred such that they are low in psychoactive chemicals like THC. Strains used in medicine are often bred for high CBD content, and strains used for recreational purposes are usually bred for high THC content, or for a specific chemical balance. Some strains of more than 20% THC have been created.

Quantitative analysis of a plant's cannabinoid profile is usually determined by gas chromatography (GC), or more reliably by gas chromatography combined with mass spectrometry (GC/MS). Liquid chromatography (LC) techniques are also possible, although these are often only semi-quantitative or qualitative. There have been systematic attempts to monitor the cannabinoid profile of cannabis over time, but their accuracy is impeded by the illegal status of the plant in many countries.

Cannabinoids can be administered by smoking, vaporizing, oral ingestion, transdermal patch, intravenous injection, sublingual absorption, or rectal suppository. Once in the body, most cannabinoids are metabolized in the liver, although some is stored in fat. Delta-9-THC is metabolized to 11-hydroxy-delta-9-THC, which is then metabolized to 9-carboxy-THC. Some cannabis metabolites can be detected in the body after several weeks.

Cannabinoids can be separated from the plant by extraction with organic solvents. Hydrocarbons and alcohols are often used as solvents. However, these solvents are flammable and many are toxic. Supercritical solvent extraction with carbon dioxide is an alternative technique. Although this process requires high pressures, there is minimal risk of fire or toxicity, solvent removal is simple and efficient, and extract quality can be well-controlled. Once extracted, cannabinoid blends can be separated into individual components using wiped film vacuum distillation or other distillation techniques. However, to produce high purity cannabinoids, chemical synthesis or semisynthesis is generally required.

Endogenous Cannabinoids

Endocannabinoids are naturally produced in the bodies of animals. After the first cannabinoid receptor was discovered in 1988, scientists began searching for natural compounds that activate these receptors.

In 1992, the first such compound was identified as arachidonoyl ethanolamide and named anandamide, a name derived from the Sanskrit word for bliss and amide. Anandamide is derived from the essential fatty acid arachidonic acid. It has a pharmacology similar to THC, although its chemical structure is different. Anandamide binds to both the central (CB1) and peripheral (CB2) cannabinoid receptors, and is found in nearly all tissues in a wide range of animals. It is about as potent as THC. Two analogs of anandamide, 7,10,13,16-docosatetraenoylethanolamide and homo-^{3}-linolenoylethanolamide, have similar pharmacology. All of these are members of a family of signalling lipids called N-acylethanolamides which also include the noncannabimimetic palmitoylethanolamide and oleoylethanolamide which have anti-inflammatory and orexigenic effects, respectively. Another endocannabinoid, 2-arachidonoyl glycerol, binds to both the CB1 and CB2 receptors, and is more abundant and less active than anandamide. Many N-acylethanolamides have also been identified in plant seeds and in molluscs. In 2001 was reported a third, ether-type endocannabinoid, 2-arachidonyl glyceryl ether (noladin ether), isolated from porcine brain. It binds to the CB1 cannabinoid receptor (Ki = 21.2 nM) and causes sedation, hypothermia, intestinal immobility, and mild antinociception in mice. It binds weakly to the CB2 receptor.

Endocannabinoids serve as intercellular 'messengers', signaling molecules that are released from one cell and activate the cannabinoid receptors present on other nearby cells. Although in this intercellular signaling role they are similar to the well-known monoamine neurotransmitters, such as acetylcholine, GABA or dopamine, endocannabinoids differ in numerous ways from them. Neurotransmitters are commonly small, water-soluble molecules that are contained within, and released from, tiny membrane-bound vesicles inside cells. Vesicles are often found in the tips, ‘terminals’, of long cellular branches called axons, and complex morphological and biochemical specializations mark the location from which vesicular release occurs. Endocannabinoids are lipophilic molecules that are not very soluble in water. They are not stored in vesicles, and exist as integral constituents of the membrane bilayers that make up cells. They are believed to be synthesized 'on-demand' rather than made and stored for later use. The mechanisms and enzymes underlying the biosynthesis of endocannabinoids remain elusive and continue to be an area of active research.

Conventional neurotransmitters are released from a ‘presynaptic’ cell and activate appropriate receptors on a ‘postsynaptic’ cell, where presynaptic and postsynaptic designate the sending and receiving sides of a synapse, respectively. Endocannabinoids are described as ‘retrograde’ transmitters because they most commonly travel ‘backwards’ against the usual synaptic transmitter flow. They are in effect released from the postsynaptic cell and act on the presynaptic cell, where the target receptors are densely concentrated on axonal terminals in the zones from which conventional neurotransmitters are released. Activation of cannabinoid receptors temporarily reduces the amount of conventional neurotransmitter released. This endocannabinoid mediated system permits the postsynaptic cell to control its

own incoming synaptic traffic. The ultimate effect on the endocannabinoid releasing cell depends on the nature of the conventional transmitter that is being controlled. When the release of the inhibitory transmitter, GABA, is reduced, the net effect is an increase in the excitability of the endocannabinoid-releasing cell. Conversely, when release of the excitatory neurotransmitter, glutamate, is reduced, the net effect is a decrease in the excitability of the endocannabinoid-releasing cell.

Endocannabinoids constitute a versatile system for affecting neuronal network properties in the nervous system.

Scientific American published an article in December of 2004, entitled "The Brain's Own Marijuana" discussing the endogenous cannabinoid system.

The current understanding recognizes the role that endocannabinoids play in almost every major life function in the human body. Cannabinoids act as a bioregulatory mechanism for most life processes, which reveals why medical cannabis has been cited as treatments for many diseases and ailments in anecdotal reports and scientific literature. Some of these ailments include: pain, arthritic conditions, migraine headaches, anxiety, epileptic seizures, insomnia, loss of appetite, GERD (chronic heartburn), nausea, glaucoma, AIDS wasting syndrome, depression, bipolar disorder (particularly depression-manic-normal), multiple sclerosis, menstrual cramps, Parkinson's, trigeminal neuralgia (tic douloureux), high blood pressure, irritable bowel syndrome, and bladder incontinence.

Synthetic & Patented Cannabinoids

Historically, laboratory synthesis of cannabinoids were often based on the structure of herbal cannabinoids and a large number of analogs have been produced and tested, especially in a group led by Roger Adams as early as 1941 and later in a group led by Raphael Mechoulam. Newer compounds are no longer related to natural cannabinoids or are based on the structure of the endogenous cannabinoids.

Synthetic cannabinoids are particularly useful in experiments to determine the relationship between the structure and activity of cannabinoid compounds, by making systematic, incremental modifications of cannabinoid molecules.

Other notable synthetic cannabinoids include:

- CP-55940 Produced in 1974, this synthetic cannabinoid receptor agonist is many times more potent than THC

HU-210 2-9 times as potent as THC

SR 141716A and SR 144528 CB1 and CB2 receptor antagonists, respectively

Nabilone Used as an anti-emetic in chemotherapy

Levonantradol Used as an anti-emetic and analgesic

Marinol Used as a presription medicine for appetite stimulation

Sativex A naturally based cannabis extract that contains both THC and CBD

Miscellaneous

- delta-9-Tetrahydrocannabinol (”**9**-THC, THC) and delta-8-tetrahydrocannabinol (”**8**-THC), mimic the action of anandamide, a neurotransmitter produced naturally in the body. The THCs produce the high

associated with marijuana by binding to the CB***1*** cannabinoid receptors in the brain.

- Tetrahydrocannabivarin (THCV), prevalent in certain South African and Southeast Asian strains of Cannabis. It is an antagonist of THC at CB***1*** receptors and attenuates the psychoactive effects of THC.
- Cannabidiol (CBD), non-psychoactive and not affecting psychoactivity of THC. CBD has anti-inflammatory effects. CBD is the precursor of THC and is the main cannabinoid in low-THC [Cannabis]() strains.
- Cannabinol (CBN), a degradation product of THC, produces a depressant effect
- Cannabichromene (CBC), non-psychoactive and not affecting psychoactivity of THC, a precursor of CBD and THC
- Cannabigerol (CBG), non-psychoactive

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Tetrahydrocannabinol

Tetrahydrocannabinol (THC)

Chemical name

()-(6aR,10aR)-6,6,9-trimethyl-3-pentyl-6a,7,8,10a-tetrahydro-6H-benzo[c]chromen-1-ol

Chemical formula $C_{21}H_{30}O_{2}$

Molecular mass 314.46 g/mol

Glass transition 9.3 °C

Boiling point 155-157 °C (vacuum, 0.07 mbar)

Solubility (water) 2.8 mg/L (23 °C)

Solubility (saline) 0.77 mg/L (NaCl, 0.15 M)

pKa 10.6

log P 3.78 (water @ pH 7 / octanol)

CAS number 1972-08-3

SMILES

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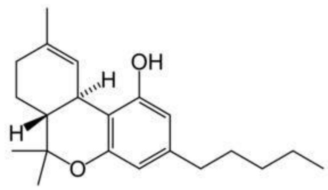

Tetrahydrocannabinol, also known as *THC*, *”***9***-THC*, *”***9***-tetrahydrocannabinol* (delta-9-tetrahydrocannabinol), *”^{1}-tetrahydrocannabinol* (using an older numbering scheme), or *dronabinol*, is the main psychoactive substance found in the Cannabis plant. It was isolated by Raphael Mechoulam and Yechiel Gaoni from the Weizmann Institute in Rehovot, Israel in 1964. In pure form it is a glassy solid when cold and becomes viscous and sticky if warmed. THC has a very low solubility in water, but a good solubility in most organic solvents such as ethanol or hexane. As in the case of nicotine and caffeine, THC's most likely function in Cannabis is to protect the plant from herbivores or pathogens [1].

Pharmacology

Its pharmacological actions are the result of its binding to the cannabinoid receptor CB1, located in the brain. The presence of these specialized receptors in the brain implied to researchers that endogenous cannabinoids were manufactured by the body, so the search began for a substance normally manufactured in the brain that binds to these receptors, the so-called natural ligand or agonist, leading to the eventual discovery of anandamide, 2 arachidonyl glyceride (2-AG) and other related compounds. This story resembles the discovery of the endogenous opiates (endorphins, enkephalins, and dynorphin), after the realization that morphine and other opiates bound to specific receptors in the brain.

THC has analgesic effects even at low doses that do not cause a "high", and cannabis was once commonly used to treat pain. Other effects include: relaxation; euphoria; altered space-time perception; alteration of visual, auditory, and olfactory senses; disorientation; fatigue; and appetite stimulation. It also has anti-emetic properties, and also may reduce aggression in certain subjects.

Toxicity

THC has a LD50 value of 1270 mg/kg (male rats) and 730 mg/kg (female rats) administered orally dissolved in sesame oil.

If this were scaled up to an adult human, the lethal dose would be between approximately 50 and 86 g for a 68 kg (150 lb) female or male person respectively. This would be equivalent to 1-1.8 kg of marijuana with a 5% THC content (roughly average) taken orally (much more if smoked). It is important to note, however, that toxicity studies in animal models do not necessarily correlate to human toxicity. THC receptor distribution in the rat CNS is different from that of humans, meaning that there is the significant possibility that toxicity in humans varies from the published animal LD***50*** studies. There has never been a documented fatality from marijuana or THC overdose.

Studies of the distribution of the cannabinoid receptors in the brain explain why THC's toxicity is so low (i.e., the LD50 of the compound is so large): parts of the brain that control vital functions such as respiration do not have many receptors, so they are relatively unaffected even by doses larger than could ever be ingested under any normal conditions.

Research

A number of studies indicate that THC may provide medical benefits for cancer and AIDS patients by increasing appetite and decreasing nausea, and by blocking the spread of some cancer-causing Herpes simplex viruses. It has been shown to assist some glaucoma patients by reducing pressure within the eye, and is used in the form of cannabis by a number of multiple sclerosis patients to relieve the spasms associated with their condition.

Studies also indicate a variety of negative effects associated with constant, long-term use, including short-term memory loss. However, other studies have refuted this, claiming the MRIs of long term users show little or no difference to MRIs of the non-using control group. The long-term effects of THC on humans have been disputed because its status as an illegal drug makes research difficult.

Preliminary research on synthetic THC has been conducted on patients with Tourette syndrome, with results suggesting that it may help in reducing nervous tics and urges by a significant degree. Animal studies suggested that Marinol and nicotine could be used as an effective adjunct to neuroleptic drugs in treating TS. Research on twelve patients showed that Marinol reduced tics with no significant adverse effects. A six-week controlled study on 24 patients showed the patients taking Marinol had a significant reduction in tic severity without serious adverse effects. Seven patients dropped out or had to be excluded from the study, one due to adverse side-effects. More significant reduction in tic severity was reported with longer treatment. No detrimental effects on cognitive functioning and a trend towards improvement in cognitive functioning were reported during and after treatment. Marinol's usefulness as a treatment for TS cannot be determined until/unless longer controlled studies on larger samples are undertaken.

Recent research has shown that many adverse side effects, generally known as the "stoner" stereotype, fail to hold up to the scientific method. Recent studies with synthetic cannabinoids show that activation of CB1 receptors can facilitate neurogeneration, as well as neuroprotection, and can even help prevent natural neural degredation from neurodegenerative diseases such as MS, Parkinson's, and Alzheimer's. This, along with research into the CB2 receptor (throughout the immune system), has given the case for medical marijuana more support.

THC, the main active component in marijuana, may protect the brain from the ravages of Alzheimer's disease, U.S. scientists reported. In lab experiments release on 10/09/2006, investigators from Scripps Research Institute in La Jolla, Calif., found THC appears to block an enzyme in the brain that causes plaques to form better than currently approved drugs.

Synthetic THC

Synthetic THC, also known under the substance name dronabinol, is available as a prescription drug (under the trade name Marinol) in several countries including the USA,

The Netherlands, and Germany. In the United States, Marinol is a Schedule III drug, available by prescription, considered to be non-narcotic and to have a low risk of physical or mental dependence. Efforts to get cannabis rescheduled as analogous to Marinol have not succeeded thus far. As a result of the rescheduling of Marinol from Schedule II to Schedule III, refills are now permitted for this substance. Marinol has been approved by the FDA in the treatment of anorexia in AIDS patients, as well as for refractory nausea and vomiting of patients undergoing chemotherapy.

An analog of dronabinol, nabilone, is available commercially in Canada under the trade name Cesamet, manufactured by Valeant. Cesamet has also received FDA approval for future availability in the United States and is a Schedule II drug.

In April 2005, Canadian authorities approved the marketing of Sativex, a mouth spray for multiple sclerosis to alleviate pain. Sativex contains tetrahydrocannabinol together with cannabidiol. It is marketed in Canada by GW Pharmaceuticals, being the first cannabis-based prescription drug in the world.

See also

- Cannabinoids
- Cannabis
- Psychoactive drug

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Chemical contraception - Hormonal contraception

Hormonal contraception refers to birth control methods that act on the hormonal system.

Currently, all hormonal contraceptives are designed for use by women rather than men, though research on a male hormonal contraceptive (“the male Pill”) has been underway for some time.

Hormonal contraceptives may be introduced into the woman’s body in many different ways, among them orally, vaginally, transdermally, or through injections or implants. The oral method was the first and most famous of these; within a few years of its introduction in 1960, "the Pill" became one of the most popular contraceptives in the United States and elsewhere, and it remains so today.

Hormonal contraception may act in one or more ways to prevent pregnancy. It may cause ovulation to cease, preventing the possibility of fertilization; it may thicken the woman’s cervical mucus, making penetration of the uterus by sperm more difficult; or it may alter and thin the endometrium so that a fertilized egg has difficulty implanting. (Technically, if the drug works in this third fashion, it acts as a contragestive rather than a contraceptive, since it has not prevented conception, acting instead to prevent gestation.)

Advantages

- If used properly, hormonal contraceptives are highly effective; except for abstinence, vasectomy, and tubal ligation, no other method of birth control has as great a degree of effectiveness.
- Hormonal contraceptives allow spontaneous intercourse.

Disadvantages

- Hormonal contraceptives offer no protection against sexually transmitted infections, placing non-monogamous individuals and couples at high risk for contracting such an infection.
- Like many other forms of birth control, hormonal contraceptives rely on the woman to use them correctly. Some, such as implants, require relatively little attention; others, such as injections or transdermal patches, require a schedule ranging from a week to several months. Still others—the wide varieties of oral contraception require a daily schedule. For example, many patient information leaflet for these pharmaceuticals suggest using a back up method of birth control if 2 or more doses are missed.[1]
- Hormonal contraceptives can have side effects, including: weight gain, loss of libido, hair loss, mood swings, bleeding between periods, nausea, breast tenderness, headaches, mastalgia, depression, ovarian cysts, constant bleeding (metrorrhagia), panic attacks, muscle pain, heart palpitations, pain during sex,

acne, abdominal cramps, dizziness, weakness or fatigue, leg cramps, nausea, vaginal discharge or irritation, bloating, swelling of the hands or feet, backache,insomnia, pelvic pain, rash, hot flashes,joint pain, convulsions, jaundice, urinary tract infections, and allergic reactions.

- Hormonal contraceptives can have serious health risks, such as ectopic pregnancy, decreased bone density, deep vein thrombosis, pulmonary embolus, uterine perforation, blood clot/stroke (stroke intensified risk for women who smoke) and death.
- Artificial contraception is objectionable to some religious traditions. These objections are furthered by the suggested, yet unproven post-fertilisation mode of action of preventing the implantation of a blastocyst.
- Hormonal contraceptives require a prescription in the United States and most other countries because of potential health risks.

Effects on rates of cancers

There is a mixed effect of combined hormonal contraceptives on the rates of various cancers, with the International Agency for Research on Cancer (IARC) concluding that "Combined oral contraceptives are carcinogenic to humans" and that "there is also conclusive evidence that these agents have a protective effect against cancers of the ovary and endometrium":[2]

- The (IARC) note that "the weight of the evidence suggests a small increase in the relative risk for breast cancer among current and recent users" which following discontinuation then lessens over a period of 10 years to similar rates as women who never used them.
- Small increases are also seen in the rates of cervical cancer and hepatocellular (liver) tumours.
- Endometrial and ovarian cancer risks are approximately halved and persists for at least 10 years after cessation of use; although "sequential oral contraceptives which were removed from the consumer market in the 1970s was associated with an increased risk for endometrial cancer".
- Studies have overall not shown effects on the relative risks for colorectal, malignant melanoma or thyroid cancers.
- Numerous studies have shown carcinogenicity in experimental animals.

Types of Hormonal Contraception

Oral Contraceptives

- Combined oral contraceptive pill -- known colloquially as "The Pill", it is a combined estrogen and progesterone pill which is taken daily at the same time.
- Progesterone only pill (POP)

Non-surgical devices

- Contraceptive patch - an adhesive patch containing hormones which is applied to the skin and worn continuously. It is changed each week for three weeks and removed for one week.
- Contraceptive vaginal ring ("NuvaRing") - a flexible ring containing estrogen and progesterone, it is inserted into the vagina and worn for three continuous weeks, removed for one week, then replaced with a new ring.

Surgical devices

- Implants - a set of small, flexible rods which contain progesterone, which are implanted under the skin. Norplant, an implant of this type, is being phased out of production, though Implanon, a newer implant, was approved in July of 2006, and Jadelle was approved in 1996.[3]
- Progesterone IntraUterine System - otherwise known as the IUS, this device is inserted into the uterus by a health care professional, where it continuously releases progesterone. It remains in the uterus for a period of years, as determined by the manufacturer.

Injections

- Lunelle - a monthly injection of progesterone, not currently available for sale.
- Depo Provera - an injection of progesterone administered every three months.

Most combined and progesterone-only pills may also be taken in high doses as emergency contraception (also known as the morning after pill). However, unlike plain copper IUDs, hormonal IUS is not approved for emergency contraception.

Cenchroman

Centchroman is sometimes mistaken for a hormonal contraceptive, probably because it is a pill that prevents pregnancy. Although it may be correctly termed a 'weekly contraceptive pill', it is not a hormonal contraceptive. Centchroman is a Selective Estrogen Receptor Modulator, or SERM. It causes ovulation to occur sooner than it normally would, while causing the lining of the uterus to build more slowly, which, together, prevent pregnancy. Centchroman is legally available only in India.

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Depo Provera

B.C. type Hormonal

First use 1967

Failure rates *(per year)*

Perfect use 0.3%

Typical use 0.3%

Usage

Duration effect 90 days (12weeks + 5 days)

Reversibility ?-18+months

User reminders Maximum interval is just under 3 months

Clinic review 12 weeks

Advantages

Periods Usually no periods from 2nd injection

Benefits Especially if poor pill compliance. Reduced endometrial cancer risk.

Disadvantages

STD protection No

Periods Especially in 1st injection may be frequent spotting

Weight gain Yes

Risks Reduced bone density; possible risk of breast cancer, cervical cancer.

Medical notes

For those intending to start family, suggest switch 6 months prior to alternative method (eg POP) allowing more reliable return fertility.

Depo-Provera is a contraceptive or birth control product which is injected every 3 months.

It is the brand name for medroxyprogesterone acetate manufactured by Pfizer Inc. It is a hormonal birth control method containing the pregnane (17±-hydroxyprogesterone derivative) progestin medroxyprogesterone acetate, without estrogen, and is administered to women in the form of an intramuscular injection once every 11 to 13 weeks. Depo-Provera causes the ovaries to stop releasing eggs.

How it works

The mechanism of action of progestin-only contraceptives depends on the progestin activity and dose.[1][2] High dose progestin-only contraceptives, such as the injectable Depo-Provera, completely inhibit follicular development and ovulation. Like all progestin-only contraceptives, Depo-Provera also has a progestogenic effect of increasing cervical mucus viscosity, thereby inhibiting sperm penetration. In anovulatory cycles using progestin-only contraceptives, the endometrium is thin and atrophic. If the endometrium was also thin and atrophic during an ovulatory cycle, this could theoretically interfere with implantation of a blastocyst (embryo).

Benefits

- Near 100% effective at preventing pregnancy.
- Injected every 3 months. The only continuing action is to book subsequent follow-up injections every twelve weeks, and to monitor side effects to insure that they do not require medical attention.
- 80% reversible within 12 months and 95% reversible within 18 months
- Depo-Provera reduces the risk of endometrial cancer by 80%.[3][4][5] The reduced risk of endometrial cancer in Depo-Provera users is thought to be due to both the direct anti-proliferative effect of progestogen on the endometrium and the indirect reduction of estrogen levels by suppression of ovarian follicular development.[6]

Pregnancy and breastfeeding

Depo Provera may be used by breast-feeding mothers. Heavy bleeding is possible if given in the immediate postpartum time and is best delayed until six weeks after birth. It may be used within five days if not breast feeding. While a small study "showed no significant difference in birth weights or incidence of birth defects" and "no significant alternation of immunity to infectious disease caused by breast milk containing DMPA", a possible subgroup of babies with 75% higher incidence of infectious disease was seen in mothers who started Depo Provera at 2 days postpartum.[7] A larger study with longer follow-up concluded that "use of DMPA during pregnancy or breastfeeding does not adversely affect the long-term growth and development of children". This study also noted that "children with DMPA

exposure during pregnancy and lactation had an increased risk of suboptimal growth in height," but that "after adjustment for socioeconomic factors by multiple logistic regression, there was no increased risk of impaired growth among the DMPA-exposed children." "Unfavorable socioeconomic factors" may therefore result in suboptimal height for DMPA-exposed children. The study also noted that effects of DMPA exposure on puberty require further study, as so few children over the age of 10 were observed.[8]

Disadvantages and side effects

Warnings and precautions

- Takes two weeks to take effect
- Offers no protection against Sexually transmitted diseases(STDs)
- Depo Provera can affect menstrual bleeding. After a year of use, 55% of women experience amenorrhoea; after 2 years, the rate rises to 68%. In the first months of use "irregular or unpredictable bleeding or spotting, or rarely, heavy or continuous bleeding" was reported.[9] Some women may prefer amenorrhea. According to Jerilynn Prior, M.D., professor of endocrinology and metabolism at the University of British Columbia in Vancouver, and board member for the Society for Menstrual Cycle Research,"the most important thing to emphasize about menstrual suppression is that the long-term effects are simply unknown," and "allowing the one vital sign unique to women to go unmonitored...could ultimately lead to an enormous uncontrolled experiment with a woman's health." [10]
- Return to fertility may be slow. Fifty percent of women may be able to conceive in about 10 months from the last injection, but fertility may be totally suppressed in some women for up to 18 months or more.[9]
- Long-term studies of users of Depo-Provera have found slight or no increased overall risk of breast cancer. However, one subset of the study population did show an increased risk of breast cancer in recent users (Depo use in the last four years) under age 35.[9]
- Infants born to women exposed to Depo during pregnancy in one study had an 80% greater chance of dying in the first year of life.[11]

Black box warning

While it has long been known that Depo-Provera causes bone loss, it has recently been discovered that the osteoporotic effects of the injection grow worse the longer Depo-Provera is administered, last long after the injections are stopped, and may be irreversible. For this reason, on November 17, 2004 the United States Food and Drug Administration and Pfizer agreed to put a "black box warning" on Depo-Provera's label.[12] However, the WHO (World Health Organization)—which provided Depo-Provera to developing countries when the US

FDA refused to approve it for safety reasons pertaining to breast cancer—advises that the use of Depo Provera should not be restricted. [13][14]

It is unclear whether the bone density loss associated with Depo-Provera use is reversible, and if so, how completely. Three studies have suggested that bone loss is reversible after the discontinuation of Depo-Provera, although one notes that bone loss was not reversible in long-term users of Depo-Provera, and the others were conducted in part by a Pfizer consultant. [15][16][17] Other studies have suggested that the effect of Depo-Provera use on post-menopausal bone density is minimal,[18] perhaps because Depo users experience less bone loss at menopause.[19] However, as of 2006, no study has directly examined fracture risk in post-menopausal women who have used Depo-Provera; therefore, the risk is unknown. Pfizer and the FDA recommend that Depo-Provera not be used for longer than 2 years, unless there is no viable alternative method of contraception, due to concerns over bone loss.[12]

Side effects

Depo-Provera may have side effects including irregular menstrual bleeding, no mentrual bleeding, constant bleeding (metrorrhagia), severe headaches, weight gain, weight loss, panic attacks, muscle pain, heart palpitations, pain during sex, acne, abdominal cramps, dizziness, weakness or fatigue, leg cramps, nausea, vaginal discharge or irritation, breast swelling and tenderness, bloating, swelling of the hands or feet, backache, depression,insomnia, pelvic pain, no hair growth or excessive hair loss, rash, hot flashes,joint pain, convulsions, jaundice, urinary tract infections, allergic reactions, fainting, paralysis, deep vein thrombosis, and pulmonary embolus.[9]

Related studies

- A study of 819 women in one city found an association between using Depo-Provera and higher incidence of chlamydia and gonorrhea.[20]
- A study of 28 rhesus monkeys linked progesterone implants (similar to, but not identical to Depo Provera) to an eightfold increase in SIV contraction.[21] While studies have not been performed on humans or with HIV, this may suggest an enhanced risk of HIV transmission.[22]
- A study in mice found that Depo Provera may simultaneously increase susceptibility to the herpesvirus and decrease immune response to the herpesvirus. [23]
- Depo Provera, exacerbates glutamate excitotoxicity, which may render users more vulnerable to neurodegeneration. [24]

Contraindications

Women with the following conditions should not use Depo Provera:

- stroke
- currently pregnant

- current or past breast cancer
- liver problems or liver disease
- blood clots

Other uses

Depo-Provera is also used with male sex offenders as a form of chemical castration as it has the effect of drastically reducing sex drive in males.

Controversy over Approval of Depo

There is a long, controversial history regarding the approval of Depo Provera by the FDA. The original manufacturer, Upjohn, applied repeatedly for approval--which was repeatedly denied. Points in the controversy include:

- Animal testing for carcinogenicity. Depo Provera caused breast cancer tumors in dogs. Critics of the study claimed that dogs are more sensitive to artificial progesterone, and that the doses were too high to extrapolate to humans. The FDA pointed out that all substances carcinogenic to humans are carcinogenic to animals as well, and that if a substance is not carcinogenic it does not register as a carcinogen at high doses. Levels of Depo Provera which caused malignant mammary tumors in dogs were equivalent to 25 times the amount of the normal luteal phase progesterone level for dogs. (Which is lower than the pregnancy level of progesterone for dogs, and is species-specific.)[3] Depo Provera caused endometrial cancer in monkeys--2 of 12 monkeys tested, the first ever recorded cases of endometrial cancer in rhesus monkeys.[25] Speaking in comparative terms regarding animal studies of carcinogenicity for drugs, a member of the FDA's Bureau of Drugs testified at an agency Depo hearing, "...Animal data for this drug is more worrisome than any other drug we know of that is to be given to well people."
- Bias of OB-GYN committee. The OB-GYN Committee, which advised the FDA to approve Depo on the two occaisons when it was not approved, was not capable of objectivity according to senior FDA officials/a former director of the FDA bureau of drugs, because members of the committee were in "the population control business."[25]
- Cervical cancer in Upjohn/NCI studies. Cervical cancer was found to be increased as high as 9-fold in the first human studies recorded by the manufacturer and the National Cancer Institute. [26]
- Coercion and Lack of Informed Consent. Testing/use of Depo was focused almost exclusively on women of color in developing countries, (especially Thailand, during the years that it was a US sponsored military dictatorship) and poor women of color in the US, raising serious questions about coercion and lack of informed consent, particularly for the illiterate[27] and for the mentally retarded, who were given Depo long-term merely to eliminate "menstrual hygiene."[28]

- Atlanta/Grady Study. Upjohn studied the effect of Depo for 11 years in Atlanta--mostly on black women who were receiving public assistance-- but did not file any of the required follow-up reports with the FDA. Investigators who eventually visited noted that the studies were disorganized. They found that data collection was questionable, consent forms and protocol were absent; that those women whose consent had been obtained at all were not told of possible side effects. Women whose known medical conditions indicated that use of Depo would endanger their health were given the shot. Several of the women in the study died; some of cancer, but some for other reasons, such as suicide due to depression. Over half the 13,000 women in the study were lost to followup due to sloppy record keeping. Consequently, no data from this study was usable.
- WHO Review. In 1992, the WHO presented a review of Depo in four developing countries to the FDA. The National Women's Health Network and other women's organizations testified at the hearing that the WHO was not objective--that the WHO could not advise the FDA not to approve Depo after they had already distributed it in developing countries. The WHO's objectivity has recently also been criticized for receiving donations from pharmaceutical companies.[29]. Depo was approved for use in US on the basis of the WHO review of previously submitted evidence from countries such as Thailand, evidence which the FDA had deemed insufficient and too poorly designed for assessment of cancer risk at a prior hearing. The Alan Guttmacher Institute has speculated that US approval of Depo may increase its availability and acceptability in developing countries. [30]
- FDA scientists report concern about their ability to voice scientific concern or inform the public about unsafe drugs, something they did not report in the years approval for Depo was rejected.[31]

Aftermath

- In 1995, women's health groups asked the FDA to put a moratorium on Depo Provera, and to institute informed consent forms following a universal standard.[32]
- Scientists and women's groups in India continue to oppose Depo Provera.[33]In 2002, Depo was removed from the family planning protocol in India.
- One in five black teenagers using birth control in the US uses Depo Provera--a far higher rate of use than for white teenagers. Activists claim this is because black teenagers are disproportionately targeted for the least safe contraceptives.[34]
- The Canadian Coalition on Depo-Provera, a coalition of women's health professional and advocacy groups, opposed the approval of Depo in Canada.[35] Since the approval of Depo in Canada in 1997, a $700 million dollar class action lawsuit has been filed against Pfizer.[36]

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Oral contraceptive

Combined Oral Contraceptive Pill (COCP)

Background
B.C. type Hormonal

First use 1960

Failure rates (per year)

Perfect use 0.1%

Typical use 2.15 - 8.0%

Usage

Duration effect 1-4days

Reversibility Yes

User reminders Taken within same 12hour window each day

Clinic review 6 months

Advantages

Periods Regulates, and often lighter and less painful

Benefits Reduced ovarian and endometrial cancer risk. May treat acne, PCOS, endometriosis

Disadvantages

STD protection No

Weight gain Possible

Risks Incr. DVTs, strokes, breast cancer

Medical notes

Affected by broad-spectrum antibiotics, the herb Hypericum (St.Johns Wort) and some anti-epileptics, also vomiting or diarrhoea. Caution if history migraines.

Oral contraceptives, often referred to as "the Pill", are chemicals taken by mouth to inhibit normal fertility. All act on the hormonal system. Oral contraceptives have been on the market since 1960, and enjoy great popularity. They are used by millions of women around the

world, but usage prevalence varies: one quarter of reproductive age women in the United Kingdom take the pill,[1] but only 1% of women in Japan.[2] Male oral contraceptives remain a subject of research and development.

History

By the 1930s, scientists had isolated and determined the structure of the steroid hormones and found that high doses of androgens, estrogens or Progesterone inhibited ovulation, but obtaining them from European pharmaceutical companies produced from animal extracts was extraordinarily expensive.

In 1939, Russell Marker, a professor of organic chemistry at Pennsylvania State University, developed a method of synthesizing progesterone from plant steroid sapogenins, initially using sarsapogenin from sarsaparilla which proved too expensive. After three years of extensive botanical research he discovered a much better starting material, diosgenin from inedible Mexican wild yams found in the jungles of Veracruz near Orizaba. Unable to interest his research sponsor Parke-Davis in the commercial potential of synthesizing progesterone from Mexican yams, Marker left Penn State and in 1944 co-founded Syntex with two partners in Mexico City before leaving Syntex a year later. Syntex broke the monopoly of European pharmaceutical companies on steroid hormones, reducing the price of progesterone almost 200-fold over the next eight years.[3]

Midway through 20th century, the stage was set for the development of a hormonal contraceptive, but pharmaceutical companies, universities and governments showed no interest in pursuing research.

In early 1951, reproductive physiologist Gregory Pincus, a leader in hormone research and co-founder of the Worcester Foundation for Experimental Biology (WFEB) in Shrewsbury, Massachusetts, first met American birth control movement founder Margaret Sanger at a Manhattan dinner hosted by Abraham Stone, medical director and vice president of Planned Parenthood (PPFA), who helped Pincus obtain a small grant from PPFA to begin hormonal contraceptive research. Research started on April 25, 1951 with reproductive physiologist Min Chueh Chang repeating and extending the 1937 experiments of Makepeace et al. that showed injections of progesterone suppressed ovulation in rabbits. In October 1951, G. D. Searle & Company refused Pincus' request to fund his hormonal contraceptive research, but retained him as a consultant and continued to provide chemical compounds to evaluate.

In March 1952, Sanger wrote a brief note mentioning Pincus' research to her longtime friend and supporter, suffragist and philanthropist Katharine Dexter McCormick, who visited the WFEB and its co-founder and old friend Hudson Hoagland in June 1952 to learn about contraceptive research there. Frustrated when research stalled from PPFA's lack of interest and meager funding, McCormick arranged a meeting at the WFEB on June 6, 1953 with Sanger and Hoagland where she first met Pincus who committed to dramatically expand and accelerate research with McCormick providing fifty times PPFA's previous funding.

Pincus and McCormick enlisted Harvard clinical professor of gynecology John Rock, an expert in the treatment of infertility, to lead clinical research with women. At a scientific conference in 1952, Pincus and Rock, who had known each other for many years, discovered they were using similar approaches to achieve opposite goals. In 1952, Rock induced a three-

month anovulatory "pseudo-pregnancy" state in eighty of his infertility patients with continuous gradually increasing oral doses of estrogen (diethylstilbestrol 5–30 mg/day) and progesterone (50–300 mg/day) and within the following four months an encouraging 15% became pregnant.

In 1953, at Pincus' suggestion, Rock induced a three-month anovulatory "pseudo-pregnancy" state in twenty-seven of his infertility patients with an oral 300 mg/day progesterone-only regimen for 20 days from cycle days 5–24 followed by pill-free days to produce withdrawal bleeding. This produced the same encouraging 15% pregnancy rate during the following four months without the troubling amenorrhea of the previous continuous estrogen and progesterone regimen. But 20% of the women experienced breakthrough bleeding and in the first cycle ovulation was suppressed in only 85% of the women, indicating that even higher and more expensive oral doses of progesterone would be needed to initially consistently suppress ovulation.

Pincus asked his contacts at pharmaceutical companies to send him chemical compounds with progestogenic activity. Chang screened over 200 chemical compounds in animals and found the three most promising were Syntex's norethindrone and Searle's norethynodrel and norethandrolone.

Chemists Carl Djerassi, Luis E. Miramontes and George Rosenkranz at Syntex in Mexico City had synthesized the first orally highly active progestin norethindrone in 1951.[4] Chemist Frank B. Colton at Searle in Skokie, Illinois had synthesized the orally highly active progestins norethynodrel (an isomer of norethindrone) in 1952 and norethandrolone in 1953.

In December 1954, Rock began the first tests of the ovulation-suppressing potential of 5–50 mg doses of the three oral progestins for three months (for 21 days per cycle—days 5–25 followed by pill-free days to produce withdrawal bleeding) in fifty of his infertility patients in Brookline, Massachusetts. 5 mg doses of norethindrone or norethynodrel and all doses of norethandrolone suppressed ovulation but caused breakthrough bleeding, but 10 mg and higher doses of norethindrone or norethynodrel suppressed ovulation without breakthrough bleeding and led to a 14% pregnancy rate in the following five months. Pincus and Rock selected Searle's norethynodrel for the first contraceptive trials in women citing its total lack of androgenicity versus Syntex's norethindrone's very slight androgenicity in animal tests.

Norethynodrel (and norethindrone) were subsequently discovered to be contaminated with a small percentage of the estrogen mestranol (an intermediate in their synthesis), with the norethynodrel in Rock's 1954-5 study containing 4-7% mestranol. When further purifying norethynodrel to contain less than 1% mestranol led to breakthrough bleeding, it was decided to intentionally incorporate 2.2% mestranol, a percentage that was not associated with breakthrough bleeding, in the first contraceptive trials in women in 1956. The norethynodrel and mestranol combination was given the proprietary name Enovid.

The first contraceptive trial of Enovid led by Edris Rice-Wray Carson began in April 1956 in Río Piedras, Puerto Rico. A second contraceptive trial of Enovid (and norethindrone) led by Edward T. Tyler began in June 1956 in Los Angeles. On January 23, 1957, Searle held a symposium reviewing gynecologic and contraceptive research on Enovid through 1956 and concluded Enovid's estrogen content could be reduced by 50% to lower the incidence of

estrogenic gastrointestinal side effects without significantly increasing the incidence of breakthrough bleeding.

In June 1957, the FDA approved Enovid 10 mg (9.85 mg norethynodrel and 150 µg mestranol) for menstrual disorders based on data from its use by more than 600 women. Numerous additional contraceptive trials showed Enovid at 10, 5, and 2.5 mg doses to be highly effective. On July 23, 1959, Searle filed a supplemental application to add contraception as an approved indication for 10, 5 and 2.5 mg doses of Enovid. The FDA refused to consider the application until Searle agreed to withdraw the lower dosage forms from the application. On May 9, 1960, the FDA announced it would approve Enovid 10 mg for contraceptive use, which it did on June 23, 1960, by which time Enovid 10 mg had been in general use for three years during which time, by conservative estimate, at least half a million women had used it.

Although FDA approved for contraceptive use, Searle never marketed Enovid 10 mg as a contraceptive. Nine months later, in February 1961, the FDA approved Enovid 5 mg for contraceptive use. In July 1961, Searle finally began marketing Enovid 5 mg (5 mg norethynodrel and 75 µg mestranol) to physicians as a contraceptive.

Although the FDA approved the first oral contraceptive in 1960, contraceptives were not available to married women in all states until Griswold v. Connecticut in 1965 and were not available to unmarried women in all states until Eisenstadt v. Baird in 1972.

The first published case report of a blood clot and pulmonary embolism in a woman using Enovid did not appear until November 1961, four years after its approval, by which time it had been used by over one million women. It would take almost a decade of epidemiological studies to conclusively establish an increased risk of venous thrombosis in oral contraceptive users and an increased risk of stroke and myocardial infarction in oral contraceptive users who smoke or have high blood pressure or other cardiovascular or cerebrovascular risk factors. These risks of oral contraceptives were dramatized in the 1969 book A Doctor's Case Against the Pill by feminist journalist Barbara Seaman who helped arrange the 1970 Senate hearings called by Senator Gaylord Nelson. The hearings were conducted by Senators who were all men and the witnesses in the first round of hearings were all men, leading Alice Wolfson and other feminists to protest the hearings and generate media attention. Their work led to mandating the inclusion of patient package inserts with oral contraceptives to explain their possible side effects and risks to help facilitate informed consent.[5] Today's standard dose oral contraceptives contain an estrogen dose that is one third lower than the first marketed oral contraceptive and contain lower doses of different, more potent progestins in a variety of formulations.

France

In 1967, the Neuwirth Law legalized contraception in France, including the pill. [6] The pill is the most popular form of contraception in France, especially among young women. The abortion rate has remained stable since the introduction of the pill. [7]

Japan

In Japan, lobbying from the Japan Medical Association prevented the Pill from being approved for nearly 40 years. Two main objections raised by the association were safety concerns over long-term use of the Pill, and concerns that the Pill use would lead to diminished use of condoms and thereby potentially increase sexually transmitted infection (STIs) rates.[8] Some voiced suspicions that potential loss of income due to lower abortion rates that could result from Pill use might have been a factor in the organization's objection. The association responded to its critics by pointing out that doctors would have received higher monetary compensation from prescribing pills, given Japan's national health insurance system. As of 2004, condoms accounted for 80% of birth control use in Japan, and this may explain Japan's comparably low rates of AIDS.[9]

The Pill was finally approved for use in 1999; however, the Pill prescription guidelines the government endorsed are quite stringent. They require Pill users to visit a doctor every three months for pelvic examinations and undergo tests for sexually transmitted diseases and uterine cancer. In the United States and Europe, in contrast, an annual or bi-annual clinic visit is standard for Pill users. As a possible result of the stringent regulations, very few women in Japan use the Pill.[2] For a detailed discussion of abortion and pill politics in Japan see Tiana Norgren (2001) Abortion before Birth Control.

Seasonale

Starting in 2003, women have also been able to use a three-month version of the Pill.[10] Similar to the effect of using a constant-dosage formulation and skipping the placebo weeks for three months, Seasonale gives the benefit of less frequent periods, at the potential drawback of breakthrough bleeding. Seasonique is another version in which the placebo week every three months is replaced with a week of low-dose estrogen.

Use

Oral contraceptives for women consist of a pill taken daily which contains doses of synthetic hormones (always a progestin and most often also an estrogen).

Combined oral contraceptive pills (which contain both a progestin and an estrogen) must be ingested within 12 hours of the same time each day and progesterone only pills (POPs) within 3 hours. Most brands of combined pills are packaged with 21 days of active (hormone-containing) pills followed by either 7 days of placebo pills, or instructions to not take pills for seven days. A woman on the pill will have a withdrawal bleed, or period, sometime during the placebo week. POPs are taken continuously; most women experience somewhat irregular bleeding while taking them.

If a woman just starting the pill begins taking them on the first day of her menstrual cycle (first day of red bleeding), she will have pregnancy protection from the very first pill. If a woman begins taking the pill at another time in her menstrual cycle, she must use a different form of contraception for seven days.

Mechanism of action

Several different types of 'the Pill' exist. Generally, all oral contraceptives have different synthetic estrogens and progestins, chemical analogues of the natural hormones, estradiol (an estrogen) and Progesterone (a Progestagen). An exception is the progestin only pill, which lacks estrogen and thus generally has fewer side effects than the combined pill.

The combined Pill primarily prevents pregnancy by preventing ovulation. It also has the side effect of thickening the cervical mucus, which can prevent or slow sperm entry into the uterus. In addition, the Pill thins the endometrium (the lining of the uterus).

Contraception vs Abortion debate

There are physicians and other medical professionals who point to this thinning of the endometrium as evidence that the Pill is an abortifacient.[11] This claim is based on experiences with in vitro fertilization which demonstrated that thinner uterine linings correlated with increased difficulty in getting the test-tube-fertilized blastocyst to implant. However, other physicians (including some pro-life physicians) are unconvinced that this truly does decrease the likelihood that an embryo will implant itself in the uterine lining.

In women who do not take The Pill, the uterine lining is usually unreceptive to implantation prior to ovulation. The purpose of the hormones released by the corpus luteum is to cause the endometrium to thicken and become receptive to implantation (which occurs between six and twelve days after ovulation if the ovum is fertilized). Thus, simple observations that the uterine lining is too thin to support implantation during a cycle where no ovulation has occurred is insufficient to support the claim that there is a reduced likelihood of implantation in ovulatory Pill cycles. Currently, no research has been conducted on the behavior of the endometrium in ovulatory Pill cycles.[12]

The theory that the pill has postfertilization effects is also based on some studies that found the ratio of extrauterine to intrauterine ratio of pregnancies increases by 70–1390% in women using the pill[13][14][15] although not all research reaches the same conclusions.[16] The asserted increased proportion of extrauterine pregnancies is most likely explained by interference of the pill with the normal process of implantation.

There is some controversy over the beginning of pregnancy. The medical consensus is that pregnancy begins with implantation, not fertilization. However some medical sources still define pregnancy as beginning with fertilization. Therefore, if oral contraceptives do interfere with implantation, the determination of whether oral contraceptives are abortifacients depends largely on a person's individual definition of pregnancy.

Effectiveness

The Pearl Index is often used to compare the effectiveness of various methods of contraception.[17] It is expressed as the "number of unintended pregnancies in 100 normally fertile women over the period of one year". Each method of birth control has two Pearl index numbers:

- method effectiveness: is the Pearl index number for use under perfect conditions. The method effectiveness Pearl index for the Pill has been measured as low as 0.3 and as high as 1.25, which means that under ideal conditions, anywhere from 0.3 to 1.25 out of 100 users will become pregnant during one year of perfect use (Pearl index = 0.3 to 1.25).
- user effectiveness or typical effectiveness: is the Pearl index number for use that is not consistent or always correct. The user effectiveness measured by the Pearl index for the Pill has been measured as low as 2.15 and as high as 8.0, which means that anywhere from 2.15 to 8.0 out of 100 women will become pregnant during the first year of typical use (Pearl index = 2.15 to 8.0).[18][19]

Many women occasionally forget to take the Pill daily, impairing its effectiveness. Correct use of the pill usually implies taking it every day at the same hour for 21 days, followed by a pause of seven days.

Use of other medications can prevent the Pill from working, due to interactions with the metabolism of the hormonal constituents. Diarrhea can also stop the Pill from working, because it causes the hormones to not be properly absorbed by the bowels.

Packaging

The Pill usually comes in two different packet sizes, with days marked off for a 28 day cycle. For the 21-pill packet, a pill is consumed daily for three weeks, followed by a week of no pills. For the 28-pill packet, 21 pills are taken, followed by week of placebo or sugar pills.

The purpose of the placebo pills is that the user, out of habit, can take a pill on every day of her menstrual cycle, instead of calculating the date she should start the next dose. Failure to take placebos has no effect on the effectiveness of the pill provided the regular schedule is followed. If the pill formulation is monophasic, it is possible to skip menstruation and still remain protected against conception by skipping the placebo pills and starting directly with the next packet. Attempting this with bi- or tri-phasic pill formulations carries an increased risk of breakthrough bleeding and may be undesirable. It will not, however, increase the risk of getting pregnant. The presence of placebo pills is thought to be comforting, as menstruation is a physical confirmation of not being pregnant. Breakthrough bleeding also becomes a more common side effect as a woman attempts to go longer periods of time between menstrual periods. The pills may contain an iron supplement, as iron requirements increase during menstruation.

Drug interactions

Some drugs reduce the effect of the Pill and can cause breakthrough bleeding, or increased chance of pregnancy. These include enzyme inducing drugs such as rifampicin antibiotic, barbiturates, phenytoin and carbamazepine. In addition cautions are given about broad spectrum antibiotics, such as ampicillin and doxycycline, which may cause problems "by impairing the bacterial flora responsible for recycling ethinyloestradiol from the large bowel" (BNF 2003).[20]

The traditional medicinal herb St John's Wort has also been implicated due to its upregulation of the P450 system in the liver.

Side-effects

When starting to take the Pill, the majority (about 60%) of women report no side effects at all, and the vast majority of those who do, have only minor effects.[21][22][23] Some women report slight weight gain, although most studies show that the incidences of this is about 50% and as many women experience slight weight loss. Some women also notice changes in the intensity of sexual desire, vaginal discharge and menstrual flow.

Other possible side effects are: breakthrough bleeding, unusual build-up of the uterine lining, nausea, headaches, depression, vaginitis, urinary tract infection, changes in the breasts, changes in blood pressure, skin problems, skin improvements, and gum inflammation. The insert included with each pill packet usually has a more extensive list of recognized side effects.

There is contradictory research into the risk of breast cancer.[24] There "is a small increase in the risk of having breast cancer diagnosed in current users of combined oral contraceptives and in women who had stopped use in past 10 years but there is no evidence of an increase in the risk more than 10 years after stopping use" and the nature of the identified cancers being less advanced clinically suggested a bias of screening in oral contraceptives users.[25]

Effects on sexuality

Some say the Pill may have a positive effect on a woman's sexuality. Because neither the woman (who uses the Pill) nor her partner need take any special action before or during intercourse, it makes birth control "invisible" and sex spontaneous, more natural, or both. When combined with the Pill's high degree of effectiveness, this may enable the couple, and especially the woman, to relax more easily during sex. Masters and Johnson reported more than one woman who experienced her first orgasm during intercourse shortly after going on the Pill.

However, some also say the Pill can also have a negative effect on a woman's sexuality. One doctor (Dr. John Bancroft, a senior research fellow at the Kinsey Institute at Indiana University) estimates that one in four women on the pill experience some negative sexual effect. These effects may include a decreased frequency of sexual thoughts, increased difficulty in becoming aroused, or decreased lubrication, which can make sex painful. Recent research co-authored by Dr. Irwin Goldstein (a urologist in Boston) suggests such effects may continue for up to four months after a woman stops taking the Pill.[26]

Cautions and contraindications

Oral contraceptives may influence coagulation, subtly increasing the risk of deep venous thrombosis (DVT) and pulmonary embolism, stroke and myocardial infarction (heart attack). However, estrogen contraceptives are usually only contraindicated in women with pre-existing cardiovascular disease, in women who have a familial tendency to form blood clots (such as familial factor V Leiden), women with severe obesity and/or hypercholesterolaemia (high cholesterol level) and most notably in smokers over 35.

Studies of higher-dose, estrogen-based pills have been linked to an increased risk of breast cancer, though no studies have been done on the lower-dose pills more popular today. In rare cases, high estrogen Pills may trigger benign intracranial hypertension.

In Our Sexuality, Crooks and Baur state a commonly held medical opinion about risks associated with Pill use: "In general, the health risks of oral contraceptives are far lower than those from pregnancy and birth."[27] Although widely accepted,[28] at least one organization disputes that conclusion,[29] and others have argued that comparing a contraceptive method to no method (pregnancy) is not relevant - instead, the comparison of safety should be among available methods of contraception.[30]

Non-Contraceptive Uses

The hormones in "the Pill" can be used to treat some medical conditions, such as polycystic ovary syndrome (PCOS), endometriosis, adenomyosis, anemia related to menstruation, and painful menstruation (dysmenorrhea). In addition, oral contraceptives are often prescribed as medication for mild or moderate acne.[31] The pill can also induce bleeding on a regular schedule for women bothered by irregular menstrual cycles and certain disorders where there is dysfunctional uterine bleeding.

Combined oral contraceptive use reduces the risk of ovarian cancer by 40% and the risk of endometrial cancer by 50% compared to never users. The risk reduction increases with duration of use, with an 80% reduction in risk for both ovarian and endometrial cancer with use for more than 10 years. The risk reduction for both ovarian and endometrial cancer persists for at least 20 years.[32]

Although the FDA does not officially condone the use of the Pill as a minor breast enhancer, many women have gone on the pill in order to increase their breast size. This results from the low doses of estrogen present along with the progestin. Results vary widely.

Social and cultural impact

Introduced at the beginning of the tumultuous decade of the 1960s, the Pill had a big social impact. In the first place, it was far more effective than any previous method of birth control, giving women unprecedented control over their fertility. Its use was separate from intercourse, requiring no special preparations at the time of sexual activity that might interfere with spontaneity or sensation. This combination of factors served to make the Pill immensely popular within a few years of its introduction.[33][34]

Because the Pill was so effective, and soon so widespread, it also heightened the debate about the moral and health consequences of pre-marital sex and promiscuity. Never before had sexual activity been so divorced from reproduction. For a couple using the Pill, intercourse became purely an expression of love, or a means of physical pleasure, or both; but it was no longer a means of reproduction. While this was true of previous contraceptives, their relatively high failure rates and their less widespread use failed to emphasize this distinction as clearly as did the Pill. The spread of oral contraceptive use thus led many religious figures and institutions to debate the proper role of sexuality and its relationship to procreation. The Catholic Church in particular, after studying the phenomenon of oral contraceptives, re-emphasized traditional Catholic teaching on birth control in the 1968

papal encyclical Humanae Vitae. The encyclical, which reiterated the traditional Catholic teaching that artificial contraception distorted the nature and purpose of sex, was greeted with open dissent by many Catholics, which contributed to the rise of a culture of dissent in following years on other Catholic teachings.[35]

A backlash against oral contraceptives occurred in the early and mid-1970s, when reports and speculations appeared that linked the use of the Pill to breast cancer. Until then, many women in the feminist movement had hailed the Pill as an "equalizer" that had given them the same sexual freedom as men had traditionally enjoyed. This new development, however, caused many of them to denounce oral contraceptives as a male invention designed to facilitate male sexual freedom with women at the cost of health risk to women.[36] At the same time, society was beginning to take note of the impact of the Pill on traditional gender roles. Women now did not have to choose between a relationship and a career; singer Loretta Lynn commented on this in 1975 with a song entitled "The Pill," which told the story of a married woman's use of the drug to liberate herself from her traditional role as wife and mother.

Environmental impact

Ethinylestradiol, the synthetic estrogen used in combined hormonal contraceptives, is excreted in the urine of women users. Sewage treatment processes do not remove these chemicals, and they are discharged into the water system. This form of pollution has been proven to have reproductive and other effects on aquatic organisms, including fish, frogs, and zooplankton. Feminization of male fish, even to the point of producing eggs, is one common effect. Both male and female fish experience delays in reproductive development, and changes are seen in their kidneys and livers.[37]

Footnotes

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Decongestants

A *decongestant* is a broad class of medications used to relieve nasal congestion. Generally, they work by reducing swelling of the mucous membranes in the nasal passages. The effects are not limited to the nose and these medicines can increase hypertension (blood pressure). These are normally paired with antihistamines to lessen this effect, but they don't always even each other out. These agents are usually administered topically (by the intranasal route) or orally. Examples of oral decongestants include pseudoephedrine and phenylephrine; for a full list of Wikipedia articles see the category listed below.

See also

- topical decongestant

Topical decongestants

Topical decongestants are decongestants applied directly to the nasal cavity. By applying them directly to the site of action, topical decongestants relieve nasal congestion while reducing the side effects associated with systemically-acting decongestants, such as high blood pressure. Topical decongestants should only be used by patients for a maximum of 3 days in a row, because rebound congestion may occur in the form of rhinitis medicamentosa.

Mechanism of action

Topical decongestants are vasoconstrictors, and work by constricting the blood vessels within the nasal cavity.

Examples of topical decongestants

- Ephedrine
- Oxymetazoline

Phenylephrine
Pseudoephedrine hydrochloride
Tramazoline
Xylometazoline
=

See also

- Decongestant

Chemotherapeutic agents

Chemotherapy is the use of chemical substances to treat disease. In its modern-day use, it refers primarily to cytotoxic drugs used to treat cancer.

In its non-oncological use, the term may also refer to antibiotics (antibacterial chemotherapy). In that sense, the first modern chemotherapeutic agent was Paul Ehrlich's arsphenamine, an arsenic compound discovered in 1909 and used to treat syphilis. This was later followed by sulfonamides discovered by Domagk and penicillin G discovered by Alexander Fleming.

Other uses of cytostatic chemotherapy agents (including the ones mentioned below) are the treatment of autoimmune diseases such as multiple sclerosis and rheumatoid arthritis, the treatment of some chronic viral infections such as Hepatitis, and the suppression of transplant rejections (see immunosuppression and DMARDs).

History

The era of chemotherapy began in the 1940s with the first uses of nitrogen mustards and folic acid inhibitors. Cancer drug development since then has exploded into a multi-billion dollar industry. The targeted-therapy revolution has arrived, but the principles and limitations of chemotherapy discovered by the early researchers still apply.

Principles

Cancer is the uncontrolled growth of cells due to damage to DNA (mutations) and, occasionally, due to an inherited propensity to develop certain tumours. Autoimmune diseases arise from an overactive immune response of the body against substances and tissues normally present in the body - in other words, the body attacks its own cells. In contrast, transplant rejection happens because a normal healthy human immune system can distinguish foreign tissues and attempts to destroy them. Also the reverse situation, called graft-versus-host disease, may take place.

Broadly, most chemotherapeutic drugs work by impairing mitosis (cell division), effectively targeting fast-dividing cells. As these drugs cause damage to cells they are termed cytotoxic. Some drugs cause cells to undergo apoptosis (so-called "cell suicide").

Unfortunately, scientists have yet to be able to locate specific features of malignant and immune cells that would make them uniquely targetable (barring some recent examples, such as the Philadelphia chromosome as targeted by imatinib). This means that other fast dividing cells such as those responsible for hair growth and for replacement of the intestinal epithelium (lining) are also affected. However, some drugs have a better side-effect profile than others, enabling doctors to adjust treatment regimens to the advantage of patients in certain situations.

As chemotherapy affects cell division, tumours with high growth fractions (such as acute myelogenous leukemia and the lymphomas, including Hodgkin's disease) are more sensitive

to chemotherapy, as a larger proportion of the targeted cells are undergoing cell division at any time.

Chemotherapeutic drugs affect "younger" tumours (i.e. less differentiated) more effectively, because at a higher grade of differentiation, the propensity to growth usually decreases. Near the center of some solid tumours, cell division has effectively ceased, making them insensitive to chemotherapy. Another problem with solid tumours is the fact that the chemotherapeutic agent often does not reach the core of the tumour. Solutions to this problem include radiation therapy (both brachytherapy and teletherapy) and surgery.

Types

The majority of chemotherapeutic drugs can be divided in to: alkylating agents, antimetabolites, anthracyclines, plant alkaloids, topoisomerase inhibitors, and antitumour agents. All of these drugs affect cell division or DNA synthesis and function in some way.

Some newer agents don't directly interfere with DNA. These include the new tyrosine kinase inhibitor imatinib mesylate (Gleevec® or Glivec®), which directly targets a molecular abnormality in certain types of cancer (chronic myelogenous leukemia, gastrointestinal stromal tumors).

In addition, some drugs may be used which modulate tumor cell behaviour without directly attacking those cells. Hormone treatments fall into this category of adjuvant therapies.

Where available, Anatomical Therapeutic Chemical Classification System codes are provided for the major categories.

Alkylating agents (L01A)

Alkylating agents are so named because of their ability to add alkyl groups to many electronegative groups under conditions present in cells. Cisplatin and carboplatin, as well as oxaliplatin are alkylating agents.

Anti-metabolites (L01B)

Anti-metabolites masquerade as purine ((azathioprine, mercaptopurine)) or pyrimidine - which become the building blocks of DNA. They prevent these substances becoming incorporated in to DNA during the "S" phase (of the cell cycle), stopping normal development and division. They also affect RNA synthesis. Due to their efficiency, these drugs are the most widely used cytostatics.

Plant alkaloids and terpenoids (L01C)

These alkaloids are derived from plants and block cell division by preventing microtubule function. Microtubules are vital for cell division and without them it can not occur. The main examples are vinca alkaloids and taxanes.

Vinca alkaloids (L01CA)

Vinca alkaloids bind to specific sites on tubulin, inhibiting the assembly of tubulin into microtubules (M phase of the cell cycle). They are derived from the Madagascar periwinkle, Catharanthus roseus (formerly known as Vinca rosea). The vinca alkaloids include:

- Vincristine

Vinblastine
Vinorelbine
Vindesine

Podophyllotoxin (L01CB)

Podophyllotoxin is a plant-derived compound used to produce two other cytostatic drugs, etoposide and teniposide. They prevent the cell from entering the G1 phase (the start of DNA replication) and the replication of DNA (the S phase). The exact mechanism of its action still has to be elucidated.

The substance has been primarily obtained from the American Mayapple (Podophyllum peltatum). Recently it has been discovered that a rare Himalayan Mayapple (Podophyllum hexandrum) contains it in a much greater quantity, but as the plant is endangered, its supply is limited. Studies have been conducted to isolate the genes involved in the substance's production, so that it could be obtained recombinantively.

Taxanes (L01CD)

Taxanes are derived from the Yew Tree. Paclitaxel is derived from the bark of the European Yew Tree while Docetaxel is derived from the pine needle of the Pacific Yew Tree. Taxanes enhance stability of microtubules, preventing the separation of chromosomes during anaphase. Taxanes include:

- Paclitaxel

Docetaxel

Topoisomerase inhibitors (L01CB and L01XX)

Topoisomerases are essential enzymes that maintain the topology of DNA. Inhibition of type I or type II topoisomerases interferes with both transcription and replication of DNA by upsetting proper DNA supercoiling.

- Some type I topoisomerase inhibitors include camptothecins: irinotecan and topotecan.
- Examples of type II inhibitors include amsacrine, etoposide, etoposide phosphate, and teniposide. These are semisynthetic derivatives of epipodophyllotoxins, alkaloids naturally occurring in the root of mayapple (Podophyllum peltatum).

Antitumour antibiotics (L01D)

The most important immunosuppressant from this group is dactinomycin, which is used in kidney transplantations.

Hormonal therapy

Several malignancies respond to hormonal therapy. Strictly speaking, this is not chemotherapy. Cancer arising from certain tissues, including the mammary and prostate glands, may be inhibited or stimulated by appropriate changes in hormone balance.

- Steroids (often dexamethasone) can inhibit tumour growth or the associated edema (tissue swelling), and may cause regression of lymph node malignancies.
- Prostate cancer is often sensitive to finasteride, an agent that blocks the peripheral conversion of testosterone to dihydrotestosterone.
- Breast cancer cells often highly express the estrogen and/or progesterone receptor. Inhibiting the production (with aromatase inhibitors) or action (with tamoxifen) of these hormones can often be used as an adjunct to therapy.
- Gonadotropin-releasing hormone agonists (GnRH), such as goserelin possess a paradoxic negative feedback effect followed by inhibition of the release of FSH (follicle-stimulating hormone) and LH (luteinizing hormone), when given continuously.

Some other tumours are also hormone dependent, although the specific mechanism is still unclear.

Dosage

Dosage of chemotherapy can be difficult: if the dose is too low, it will be ineffective against the tumor, while at excessive doses the toxicity (side-effects, neutropenia) will be intolerable to the patient. This has led to the formation of detailed "dosing schemes" in most hospitals, which give guidance on the correct dose and adjustment in case of toxicity. In immunotherapy, they are in principle used in smaller dosages than in the treatment of malign diseases.

In most cases, the dose is adjusted for the patient's body surface area, a composite measure of weight and height that mathematically approximates the body volume. The BSA is usually calculated with a mathematical formula or a nomogram, rather than by direct measurement.

Delivery

Most chemotherapy is delivered intravenously, although there are a number of agents that can be administered orally (e.g. melphalan, busulfan,capecitabine). Depending on the patient, the cancer, the stage of cancer, the type of chemotherapy, and the dosage,

intravenous chemotherapy may be given on either an inpatient or outpatient basis. For continuous, frequent or prolonged intravenous chemotherapy administration, various systems may be surgically inserted into the vasculature to maintain access. Commonly used systems are the Hickman line, the Port-a-Cath or the PICC line. These have a lower infection risk, are much less prone to phlebitis or extravasation, and abolish the need for repeated insertion of peripheral cannulae.

Treatment schemes

There are a number of strategies in the administration of chemotherapeutic drugs used today. Chemotherapy may be given with a curative intent or it may aim to prolong life or to palliate symptoms.

Combined modality chemotherapy is the use of drugs with other cancer treatments, such as radiation therapy or surgery. Most cancers are now treated in this way. Combination chemotherapy is a similar practice which involves treating a patient with a number of different drugs simultaneously. The drugs differ in their mechanism and side effects. The biggest advantage is minimising the chances of resistance developing to any one agent.

In neoadjuvant chemotherapy (preoperative treatment) initial chemotherapy is aimed for shrinking the primary tumour, thereby rendering local therapy (surgery or radiotherapy) less destructive or more effective.

Adjuvant chemotherapy (postoperative treatment) can be used when there is little evidence of cancer present, but there is risk of recurrence. This can help reduce chances of resistance developing if the tumour does develop. It is also useful in killing any cancerous cells which have spread to other parts of the body. This is often effective as the newly growing tumours are fast-dividing, and therefore very susceptible.

Palliative chemotherapy is given without curative intent, but simply to decrease tumor load and increase life expectancy. For these regimens, a better toxicity profile is generally expected.

Most chemotherapy regimens require that the patient is capable to undergo the treatment. Performance status is often used as a measure to determine whether a patient can receive chemotherapy, or whether dose reduction is required.

Side-effects

The treatment can be physically exhausting for the patient. Current chemotherapeutic techniques have a range of side effects mainly affecting the fast-dividing cells of the body. Important common side-effects include (dependent on the agent):

- Hair loss
- Nausea and vomiting
- Diarrhea or constipation
- Anemia
- Depression of the immune system hence (potentially lethal) infections and sepsis
- Hemorrhage
- Secondary neoplasms
- Cardiotoxicity
- Hepatotoxicity

Nephrotoxicity
Ototoxicity

Immunosuppression and myelosuppression

Virtually all chemotherapeutic regimens can cause depression of the immune system, often by paralysing the bone marrow and leading to a decrease of white blood cells, red blood cells and platelets. The latter two, when they occur, are improved with blood transfusion. Neutropenia (a decrease of the neutrophil granulocyte count below 0.5 x 109/litre) can be improved with synthetic G-CSF (granulocyte-colony stimulating factor, e.g. filgrastim, lenograstim, Neupogen®, Neulasta®.)

In very severe myelosuppression, which occurs in some regimens, almost all the bone marrow stem cells (cells which produce white and red blood cells) are destroyed, meaning allogenic or autologous bone marrow cell transplants are necessary. (In autologous BMTs, cells are removed from the patient before the treatment, multiplied and then re-injected afterwards; in allogenic BMTs the source is a donor.) However, some patients still develop diseases because of this interference with bone marrow.

Nausea and vomiting

Nausea and vomiting caused by chemotherapy; stomach upset may trigger a strong urge to vomit, or forcefully eliminate what is in the stomach.

Stimulation of the vomiting center results in the coordination of responses from the diaphragm, salivary glands, cranial nerves, and gastrointestinal muscles to produce the interruption of respiration and forced expulsion of stomach contents known as retching and vomiting. The vomiting center is stimulated directly by afferent input from the vagal and splanchnic nerves, the pharynx, the cerebral cortex, cholinergic and histamine stimulation from the vestibular system, and efferent input from the chemoreceptor trigger zone (CTZ). The CTZ is in the area postrema, outside the blood-brain barrier, and is thus susceptible to stimulation by substances present in the blood or cerebral spinal fluid. The neurotransmitters dopamine and serotonin stimulate the vomiting center indirectly via stimulation of the CTZ.

The 5-HT3 inhibitors are the most effective antiemetics and constitute the single greatest advance in the management of nausea and vomiting in patients with cancer. These drugs are designed to block one or more of the signals that cause nausea and vomiting. The most sensitive signal during the first 24 hours after chemotherapy appears to be 5-HT3. Blocking the 5-HT3 signal is one approach to preventing acute emesis (vomiting), or emesis that is severe, but relatively short-lived. Approved 5-HT3 inhibitors include: dolasetron (Anzemet®), granisetron (Kytril®), and ondansetron (Zofran®). The newest 5-HT3 inhibitor, Aloxi® (palonosetron), has a distinct advantage over the other 5-HT3 inhibitors because, in addition to preventing acute nausea and vomiting, Aloxi® also prevents delayed nausea and vomiting, which occurs during the 2-5 days after treatment. Aloxi® is the only drug in its class that is approved by the FDA for the treatment of delayed nausea and vomiting.

Some studies[1] and patient groups claim that the use of cannabinoids derived from marijuana during chemotherapy greatly reduces the associated nausea and vomiting, and enables the patient to eat. Some synthetic derivatives of the active substance in marijuana (tetrahydrocannabinol or THC) such as Marinol may be practical for this application.

Other side effects

In particularly large tumors, such as large lymphomas, some patients develop tumor lysis syndrome from the rapid breakdown of malignant cells. Although prophylaxis is available and is often initiated in patients with large tumors, this is a dangerous side-effect which can lead to death if left untreated.

A proportion of patients reports fatigue or non-specific neurocognitive problems, such an inability to concentrate; this is colloquially referred to as "chemo brain" by patients' groups[2]

Chemotherapy may increase the risk of cardiovascular disease and occasionally leads to secondary cancer.

See also

- Gene therapy

References

1. ^ Tramer MR, Carroll D, Campbell FA, Reynolds DJ, Moore RA, McQuay HJ. Cannabinoids for control of chemotherapy induced nausea and vomiting: quantitative systematic review. BMJ 2001;323:16-21. PMID 11440936.
2. ^ Tannock IF, Ahles TA, Ganz PA, Van Dam FS. Cognitive impairment associated with chemotherapy for cancer: report of a workshop. J Clin Oncol 2004;22:2233-9. PMID 15169812.

Angiogenesis inhibitors

An *angiogenesis inhibitor* is a drug or a dietary component that inhibits angiogenesis (the growth of new blood vessels).

Known inhibitors include the drug bevacizumab which binds vascular endothelial growth factor (VEGF), inhibiting its binding to the receptors that promote angiogenesis. Some common components of the Oriental diet (and to a much lesser extent, the Western diet) also act as mild angiogenesis inhibitors. In particular, the following foodstuffs contain significant inhibitors and have been suggested as part of a healthy diet for this and other benefits:

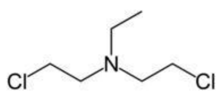
- Soy products such as tofu and tempeh, (which contain the inhibitor "genistein")

Chinese cabbage (brassinin)
Green tea (catechins)
Red Wine (resveratrol) - Suggested only in moderation

Research and development in this field has been driven largely by the desire to find better cancer treatments. Tumors can grow only if they form new blood vessels. By stopping the growth of blood vessels, scientists hope to shut off the means by which tumors can extend themselves and spread inside the body. In animal studies, angiogenesis inhibitors have successfully stopped the formation of new blood vessels.

In addition to their use as anti-cancer drugs, angiogenesis inhibitors are being investigated for their use in weight loss, as blood vessels in adipose tissue never fully mature, and are thus destroyed by angiogenesis inhibitors.

Nitrogen mustard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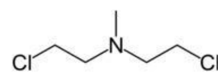
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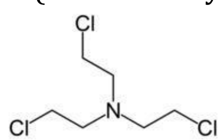

HN3 (tris(2-chloroethyl)amine)

The *nitrogen mustards* are cytotoxic chemotherapy agents similar to mustard gas. Although their common use is medicinal, in principle these compounds may also be used for chemical warfare purposes.

The prototype nitrogen mustard drug is mustine which is no longer commonly in use but was the first drug to be used as an anticancer chemotherapeutic. It is a schedule 1 substance in the Chemical Weapons Convention. Other nitrogen mustards include cyclophosphamide, chlorambucil, uramustine and melphalan.

Nitrogen mustards act by exerting radiomimetic properties on the cytogenetic material of the cell (chromosomes) ie; the effects seen are similar to genetic material which has been exposed to radiation.

Ovation Pharma bought the rights to nitrogen mustard . A New York Times article has mentioned that only about 5000 people use therapeutic nitrogen mustard in the United States.

Examples of nitrogen mustards that can be used for chemical warfare purposes and their military weapon designations include:

- HN1: Bis(2-chloroethyl) ethylamine

HN2: Bis(2-chloroethyl) methylamine
HN3: Tris(2-chloroethyl) amine

All belligerent nations stock-piled large amounts of munitions containing nitrogen mustard gas during the Second World War, but none were used in combat. As with all types of mustard gas, nitrogen mustard is a powerful and persistent blister agent.

Dietary supplements

A prescribed *dietary supplement* is intended to supply nutrients (vitamins, minerals, fatty acids or amino acids) that are missing or not consumed in sufficient quantity in a person's diet. This may include *herbal supplements* which have a history of claims that they cure or prevent certain diseases. The medical utility and regulatory status of dietary supplements is controversial.

United States

In the United States, a *dietary supplement* is defined under the *Dietary Supplement Health and Education Act of 1994*[1] as a product that meets each of the following criteria:

1. It is intended to supplement the diet and bears or contains one or more of the following dietary ingredients:
    - **a** vitamin**,**
    - a mineral,
    - an herb or other botanical (excluding tobacco),
    - an amino acid,
    - a dietary substance for use by man to supplement the diet by increasing the total daily intake (e.g., enzymes or tissues from organs or glands),
    - a concentrate, such as a meal replacement or energy bar, or
    - a metabolite, constituent, or extract.
2. It is intended for ingestion in pill, capsule, tablet, or liquid form.
3. It is not represented for use as a conventional food or as the sole item of a meal or diet.
4. It is labeled as a "dietary supplement".

The FDA regulates dietary supplements as foods, and not as drugs. The FDA does not pre-approve dietary supplements on their safety and efficacy, unlike drugs. In contrast, the FDA can only go after dietary supplement manufacturers after they have put unsafe products on the market. However, certain foods (such as infant formula and medical foods) are deemed special nutritionals because they are consumed by highly vulnerable populations and are thus regulated more strictly than the majority of dietary supplements.

The claims that a dietary supplement makes are essential to its classification. If a dietary supplement claims in any way to cure, mitigate, or treat a disease, it would be considered to be an unauthorized new drug and in violation of the applicable regulations and statutes. As the FDA states it in a response to this question in a FAQ:

Is it legal to market a dietary supplement product as a treatment or cure for a specific disease or condition?

No, a product sold as a dietary supplement and promoted on its label or in labeling* as a treatment, prevention or cure for a specific disease or condition would be considered an unapproved--and thus illegal--drug. To maintain the product's status as a dietary supplement, the label and labeling must be consistent with the provisions in the Dietary Supplement Health and Education Act (DSHEA) of 1994.

***Labeling refers to the label as well as accompanying material that is used by a manufacturer to promote and market a specific product.**

Dietary supplements are permitted to make structure/function claims. These are broad claims that the product can support the structure or function of the body (e.g., "glucosamine helps support healthy joints"). The FDA must be notified of these claims within 30 days of their first use, and there is a requirement that these claims be substantiated. Nevertheless, many critics claim that dietary supplements overstate their importance and their impact on overall health. Evidence of many of the claimed benefits of certain dietary supplements has yet to meet standard scientific criteria of credibility, based on large scale, double blind testing with statistically significant outcomes.

Other claims that required approval from FDA include health claims and qualified health claims. Health claims are permitted to be made if they meet the requirements for the claims found in the applicable regulations. Qualified health claims can be made through a petition process, including scientific information, if FDA has not approved a prior petition.

European Union

The *Food Supplements Directive*[2] requires that supplements be demonstrated to be safe, both in quantity and quality. Some vitamins are essential in small quantities but dangerous in large quantities. Some herbal remedies, notably St Johns Wort, may interact with drugs or render them less effective. Such an issue has been raised in the case of oral contraceptives. Consequently, only those supplements that have been proven to be safe may be sold without prescription. In practice, the number of reported incidents with food supplements is nevertheless low.

In Europe, it is also an established notion that food supplements should not be labeled with drug claims but can bear -to a degree that differs from one member state to the other-health claims.

Legal challenge

The dietary supplements industry in Europe strongly opposed the Directive. A large number of consumers throughout Europe, including over one million in the UK, and many doctors and scientists, have signed petitions against what are viewed by the petitioners as unjustified restrictions of consumer choice [3]. The European Court of Justice ruled[4] on 12 July 2005 that the Directive is valid, although the court's own Advocate General advised that the declaration was invalid under EU law [3]. The court made clear, however, that it must be possible for manufacturers to add vitamins and minerals to the list of ingredients of a food supplement, that refusal must be on scientific grounds, and that there should be a right to appeal.

Russia

Russian legislation, Ministry of Health's order 117 dated as of 15 April, 1997, under the title “Concerning the procedure for the examination and health certification of Biologically Active Dietary Supplements”, provides the usage of the following terminology:

As a rule, BADSs are foodstuffs with clinically proven effectiveness. BADSs are recommended not only for prophylactics, but can be included into a complex therapy for the prevention of pharmaceutical therapy's side effects and for the achievement of complete remission.

The development of BADSs and their applications has been very fast moving. They were originally considered as dietary supplements for people who had heightened requirements for some normal dietary components (for example, sportsmen). Later, they were employed as preventive medicines against chronic diseases.

Notes

1. ^ US Dietary Supplement Health and Education Act of 1994
2. ^ Directive 2002/46/EC of the European Parliament and of the Council of 10 June 2002 on the approximation of the laws of the Member States relating to food supplements
3. **^** a b "Controversial EU vitamins ban to go ahead" (the Times, July 12 2005)
4. ^ The Court confirms the validity of the Community Directive on food supplements (Press release)

See also

- Vitamin

Energy drinks

Energy drinks are beverages that are designed to give the consumer a burst of energy by using a combination of methylxanthines, B vitamins, and exotic herbal ingredients. Energy drinks commonly include caffeine, guarana (extracts from the guarana plant), taurine, various forms of ginseng, maltodextrin, inositol, carnitine, creatine, glucuronolactone and ginkgo biloba. Some contain high levels of sugar, or glucose while most brands also offer an artificially sweetened version. Often manufacturers add a very small dose of a powerful stimulant such as carnitine, but the doses of these add-ins are usually so small that any added “boost” is purely psychological. These drinks are typically marketed towards young people, students, people 'on the go' and those who play sports.

History

Jolt Cola was released in the 1980s. It was not an energy drink but a high-caffeine, high-sugar brand of cola. It pioneered a marketing strategy still widely in use by energy drinks today, targeting a generally younger audience, mostly students and young professionals (people on-the-go), billing itself as something that was not necessarily healthy but which would allow them to cram more hours into their day. Later, marketing turned further and further toward people involved in the technology industry, and consequently, energy drinks today are commonly associated with the image of a hacker or IT professional, sitting up late at his or her computer trying to stay awake. The recent energy drink phenomenon in North America seemed to follow the sudden popularity of Red Bull, which still has roughly 70% of the market share . Major players such as Pepsi, Coca-Cola, Molson and Labatt have tried to match the small companies' innovative and different approach with marginal success.

In Japan, the energy drink phenomenon dates at least as far back as the early 1960s, with the release of the Lipovitan D drink from Taisho Pharmaceuticals. Most such products in Japan bear little resemblance to soft drinks, and are sold instead in small brown glass medicine bottles or cans styled to resemble such containers. These "genki drinks" are marketed primarily to the salaryman set, to help them work long hours, or to stay awake on the late commute home.

In the beginning of the 21st century, the addition of energy components into alcoholic beverages made an impact on the market. Many malt beverages such as Sparks, 3sum malt beverage, and Max capitalized on the effects of caffeine while drinking alcohol.

Energy drinks are different from sports drinks. Most energy drinks simply provide lots of sugar or caffeine. Sports drinks are intended to replenish electrolytes, sugars, water and other nutrients and are usually isotonic (containing the same proportions as found in the human body). Some products are now available as hybrids between energy drinks and sport drinks, having electrolytes (sport drinks, aka as isotonic beverages) and herbal extracts (energy drinks) such as Reload and Vault (soft drink).

Criticism

Addiction potential

The only possible physically addictive ingredients in most of these drinks are caffeine and guarana, which cause physical addiction in large doses or with prolonged use (quantities in energy drinks are comparable to amounts in coffee). Since withdrawal from both is usually mild, mainly involving headaches, addiction to energy drinks is mostly psychological.

Parents' groups have criticized energy drinks as being irresponsibly marketed to youth, citing possible health hazards (see below), but to date, very few fatalities have been reported from overconsumption of energy drinks.

Health hazard

Little conclusive research have been published so far on the health hazards of energy drinks. However, their high concentration in ingredients such as caffeine and taurine worries certain parents and some medical specialists who suspect that long term use may cause unwanted side-effects. The Red Bull article section has more information on mortality and dental risks. On the other hand, there is no consensus on the existence or lack of health benefits as well. [1] [2][3] [4][5]

Table of energy drinks

A table of energy drinks follows, with a few coffee variants, and some soft drinks such as Bawls, Coca-Cola, Mountain Dew, and Pepsi listed for comparison, and marked in a different color. Note that caffeine content in coffee flavors varies, depending on both caffeine content and how the coffee beans were roasted. Source of some data listed below: Energy Fiend.

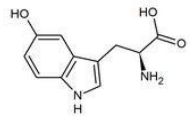
Energy drink	Caffeine (mg/fl oz)	mg/l	per serving (quantity)
Bawls	6.70	223	56 mg (8.4 fl oz/250 ml)
Coca-Cola	2.83	95	34 mg (12 fl oz/355 ml)
Cola	2.8-3.9	95-130	34-46 mg (12 oz/355 ml)
Cola (Diet)	2.83	110-141	39-50 mg (12 fl oz/355 ml)
Coffee, brewed	7-16 (varies)	230-580 (varies)	135-180 mg (8 fl oz/237 ml/1 cup)
Coffee, instant	9-14 (varies)	300-467 (varies)	71-111 mg (8 fl oz/237 ml/1 cup)
Espresso	20-50 (varies)	600-1700 (varies)	36-102 mg (2 fl oz/60 ml)
Mountain Dew	4.67	156	55 mg (12 fl oz/355 ml)
Pepsi	3.13	104	37 mg (12 fl oz/355 ml)
Tea	5-6.33	169-211	40-50 mg (8 fl oz/237 ml)

References

- Study of sleep and energy drinks. PMID 11897259

1. ^ http://ec.europa.eu/comm/food/fs/sc/scf/out22_en.html
2. ^ http://www.24x7updates.com
3. ^ http://www.hc-sc.gc.ca/iyh-vsv/food-aliment/caffeine_e.html
4. ^ http://www.freshangles.com/display/?/realtime/32/
5. ^ http://energydrinks.factexpert.com/890-energy-drink-hazards.php

5-Hydroxytryptophan



Chemical name 5-hydroxytryptophan, 5-HTP, (S)-2-amino-3-(5-hydroxy-1H-indol-3-yl)propanoic acid

Chemical formula $C_{11}H_{12}N_2O_3$

Molecular mass 220.22458 g/mol

CAS number [56-69-9]

SMILES Oc1cc2c(C[C@@](N)([H]) C(O)=O)c[nH]c2cc1

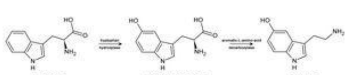
5-Hydroxytryptophan or *5-HTP* is a precursor to the neurotransmitter serotonin and an intermediate in tryptophan metabolism. It is marketed in the United States and other countries as a dietary supplement for use as an antidepressant, appetite suppressant, and sleep aid.

Pharmacology

5-Hydroxytryptophan is decarboxylated to serotonin (5-hydroxytryptamine) by the enzyme aromatic-L-amino-acid decarboxylase.

The psychoactive action of 5-HTP is thought to derive from its effect on serotonin synthesis. It is believed that an artificially high supply of 5-HTP causes the brain's serotonin-producing neurons to increase production. Increased serotonin production then leads to increased serotonin release.

Some doctors suggest that 5-HTP be administered with a peripheral decarboxylase inhibitor such as carbidopa in order to prevent elevated levels of serotonin in the bloodstream (and their side effects, which include emesis and potentially fibrosis of the heart).[1] Research shows that co-administration with carbidopa greatly increases plasma 5-HTP levels.[2]



Metabolic pathway from tryptophan to serotonin.

5-HTP as therapeutic supplement

5-HTP, which is found in infinitesimal amounts in certain foods like turkey and cheese, is often sold as an over-the-counter therapeutic supplement. In this case, it is usually sourced from the seeds of the Griffonia simplicifolia plant. Production of 5-HTP as a supplement increased when a similar serotonin-altering supplement, L-tryptophan, was banned in the United States because of a tainted batch which caused serious side-effects in users. 5-HTP has many advantages over L-tryptophan: being safer to produce and arguably more potent. 5-HTP in supplement form is usually sold in gelatin capsules. These capsules typically

contain either 50mg or 100mg of 5-HTP per capsule. It is recommended to take it on an empty stomach before falling asleep, or in smaller doses throughout the day.

Research

Some studies of 5-HTP have been completed which indicate that 5-HTP has potential in the treatment of depression and possibly anxiety, panic disorder, sleep disorders and obesity. In fact, a survey of all published studies of clinical outcomes with 5-HTP indicate that it yields similar results to those obtained for small scale studies of prescription SSRI antidepressants. Additionally, one open study suggests that people with anxious depressive syndrome may see better results from 5-HTP than from an SSRI.

It is unfortunate that the studies to date are incomplete, even if promising, for the treatment of mild to moderate depression. Reviews of these studies do indicate that potential exists for 5-HTP in the treatment of depression, but further trials are stressed as necessary before arriving at any firm conclusion. Some caution and diligence should be exhibited regarding 5-HTP barring further study and review.

Studies have also indicated miscellaneous benefits from 5-HTP supplementation in patients with fibromyalgia. Reductions in serotonergic tone are partially responsible for cognitive deficits (memory loss) resulting from tetrahydrocannibinol (THC, the active component in marijuana). When given to rats, 5-HTP can significantly attenuate THC-induced memory impairment.[3]

Uses

In recent years 5-HTP has been sold by health food companies as an alternative treatment for depression and mood disorders. Its role as an intermediary in the biosynthesis of serotonin indicates that this chemical may indeed be effective in treating these and other serotonin-related disorders, but there is some debate on the conclusions of the clinical trials which have been carried out using the drug.

5-HTP is also used as a supplement by users of MDMA (ecstasy) to help replenish depleted serotonin, in an attempt to alleviate to a degree the depression and overall mental unsettlement that sometimes occurs in the days following MDMA usage. It should be noted that a temporary decline in serotonin levels is only one of several factors in post-MDMA use cognitive disruptions; neuroadaptive changes in receptor density likely play a larger long-term role.[6] 5-HTP is less commonly used immediately before the use of MDMA as a means to both further reduce the negative psychological effects of depleted serotonin, and as an attempt to boost the effects of MDMA. Anecdotal reports seem to indicate this is largely placebo with some users reporting a moderate muting of the MDMA effect.[4]

5-HTP also has mild psychoactive effects on REM sleep and has been shown in clinical studies to relieve migraines and panic attacks .

5-HTP supplements instead of SSRIs

Natural healing practioners often recommend 5-HTP supplements instead of standard SSRI/MAOI prescriptions as 5-HTP allegedly accomplishes the same goal without resorting to disturbing the brain's natural metabolic procedures. Instead of interrupting the recycling of serotonin as in the case of SSRIs, and instead of preventing the end consumption of serotonin as in the case of MAOIs, 5-HTP supplements provide more raw material that may be used in the body's natural serotonin production process, as shown in the illustration above.

The body's usual source for manufacturing 5-HTP is tryptophan, an amino acid found in many foods, turkey being the most cited example. Tryptophan was also sold as a supplement in health food stores until a contaminated shipment, which resulted in 1500 cases of eosinophilia-myalgia syndrome and over 30 deaths, prompted the United States Food and Drug Administration to ban it as an over-the-counter supplement. As a response to this ban, health supplement producers decided to market 5-HTP in its place. Recently, however, as noted above, pharmaceutical grade L-tryptophan has become available "over the counter" in the U.S.

Dosage

Though there is no official dosage, most supplement providers recommend 50 mg or 100 mg 5-HTP, one to three times per day. Most clinical studies have tested doses of 200-300 mg/day, although one study tested doses as large as 3250 mg/day. Although many studies do not report a dosing schedule, the majority of those that do have reported using two to four doses split throughout the day.[5] Some suggest 5-HTP should be taken just before bed if taking a single daily dose, because it may cause drowsiness.

In theory, an overdose of 5-HTP could cause serotonin syndrome, although there are no reported cases of hospitalizations due to excessive ingestion of 5-HTP.[6] Nor was serotonin syndrome observed in several studies that augmented traditional antidepressant therapy with 5-HTP, even though the combination therapy was expected increase the risk of serotonin syndrome above 5-HTP alone.[5] In dogs, doses of 23.6 mg/kg were found to cause toxic reactions, although the dose response curve for dogs does not necessarily scale to humans.[7] Some users report high doses (300 mg and over) can produce nausea and vomiting.[8]

Side effects

Promoters of 5-HTP claim that it causes fewer side effects than traditional antidepressants. Side effects of 5-HTP may include nausea, constipation, gas, drowsiness, or a decreased sex drive. It can also have adverse interactions with other natural and traditional drugs.[9] Others warn that the long term effects of 5-HTP are not known, and point out that people using any psychiatric drug, natural or otherwise, should be under a doctor's supervision. [10]

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Calcium

General

Name, Symbol, Number: calcium, Ca, 20

Chemical series alkaline earth metals

Group, Period, Block 2, 4, s

Appearance silvery white

Atomic mass 40.078(4) g/mol

Electron configuration [Ar] 4s2

Electrons per shell 2, 8, 8, 2

Physical properties

phase solid

Density (near r.t.) 1.55 g·cm3

Liquid Density at m.p. 1.378 g·cm3

Melting point 1115 K (842 °C, 1548 °F)

Boiling point1757 K (1484 °C, 2703 °F)

Heat of fusion 8.54 kJ·mol1

Heat of vaporization 154.7 kJ·mol1

Heat capacity (25 °C) 25.929 J·mol1·K1

Vapor pressure

P/Pa	1	10	100	1 k	10 k	100 k
at T/K	864	956	1071	1227	1443	1755

Atomic properties

Crystal structure cubic face centered

Oxidation states 2 (strongly basic oxide)

Electronegativity 1.00 (Pauling scale)

Ionization energies 1st: 589.8 kJ·mol1, 2nd: 1145.4 kJ·mol1, 3rd: 4912.4 kJ·mol1

Atomic radius 180 pm

Atomic radius (calc.) 194 pm

Covalent radius 174 pm

Miscellaneous

Magnetic ordering paramagnetic

Electrical resistivity (20 °C) 33.6 n©·m

Thermal conductivity (300 K) 201 W·m1·K1

Thermal expansion (25 °C) 22.3 µm·m1·K1

Speed of sound (thin rod) (20 °C) 3810 m/s

Young's modulus 20 GPa

Shear modulus 7.4 GPa

Bulk modulus 17 GPa

Poisson ratio 0.31

Mohs hardness 1.75

Brinell hardness 167 MPa

CAS registry number 7440-70-2

Selected isotopes

iso	NA	half-life	DM	DE (MeV)	DP
^{40}Ca	96.941%	Ca is stable with 20 neutrons			
^{41}Ca	syn	1.03×10^{5} y	ε	-	^{41}K
^{42}Ca	0.647%	Ca is stable with 22 neutrons			
^{43}Ca	0.135%	Ca is stable with 23 neutrons			
^{44}Ca	2.086%	Ca is stable with 24 neutrons			
^{45}Ca	syn	162.7 d	β^-	0.258	^{45}Sc
^{46}Ca	0.004%	$>2.8\times10^{15}$ y	$\beta^-\beta^-$	?	^{46}Ti
^{47}Ca	syn	4.536 d	β^-	0.694, 1.99	^{47}Sc
			γ	1.297	-
^{48}Ca	0.187%	$>4\times10^{19}$ y	$\beta^-\beta^-$	?	^{48}Ti

Calcium (IPA: /ÈkalsiYm/) is the chemical element in the periodic table that has the symbol Ca and atomic number 20. It has an atomic mass of 40.078. Calcium is a soft grey alkaline earth metal that is used as a reducing agent in the extraction of thorium, zirconium and uranium. Calcium is also the fifth most abundant element in the Earth's crust. It is essential for living organisms, particularly in cell physiology, and is the most common metal in many animals.

Notable characteristics

Calcium is a rather soft, gray, metallic element that can be extracted by electrolysis from calcium fluoride. It burns with a yellow-red flame and forms a white nitride coating when exposed to air. It reacts with water, displacing hydrogen and forming calcium hydroxide.

Calcium is essential in muscle contraction, oocyte activation, bones and tooth structure, blood clotting, nerve impulse transmission, regulating heartbeat, and fluid balance within cells. In the U.S., between about 50% and 75% of adults do not get sufficient calcium in their diet.[1] Adults need between 1,000 and 1,300 mg of calcium in their daily diet.[1]

The most abundant isotope, **40**Ca, has a nucleus of 20 protons and 20 neutrons. Its electron configuration is: 2 electrons in the K shell (principal quantum number 1), 8 in the L shell (principal quantum number 2), 8 in the M shell (principal quantum number 3), and 2 in the N shell (principal quantum number 4). The outer shell is the valence shell, with 2 electrons in the lone 4s orbital, the 3d orbitals being empty.

Occurrence

Calcium is not naturally found in its elemental state. Calcium is found mostly in soil systems as limestone, gypsum and fluorite. Stalagmites and stalactites contain calcium carbonate. Being an essential macromineral in the human diet, soil conservation practices often consider the sustainable equilibrium of calcium concentrations in the earth.

Applications

Uses include:

- as a reducing agent in the extraction of other metals, such as uranium, zirconium, and thorium.
- as a deoxidizer, desulfurizer, or decarbonizer for various ferrous and nonferrous alloys.
- as an alloying agent used in the production of aluminium, beryllium, copper, lead, and magnesium alloys.
- in the making of cements and mortars to be used in construction.

History

Calcium (Latin calcis, meaning "lime") was known as early as the first century when the Ancient Romans prepared lime as calcium oxide. It was not actually isolated until 1808 in England when Sir Humphry Davy electrolyzed a mixture of lime and mercuric oxide. Davy was trying to isolate calcium and when he heard that Berzelius and Pontin prepared calcium amalgam by electrolyzing lime in mercury, he tried it himself. He worked with electrolysis throughout his life and also discovered/isolated magnesium, strontium and barium.

Compounds

Calcium, combined with phosphate to form hydroxylapatite, is the mineral portion of human and animal bones and teeth. The mineral portion of some corals can also be transformed into hydroxylapatite.

Calcium oxide (lime) is used in many chemical refinery processes and is made by heating and carefully adding water to limestone. When lime is mixed with sand, it hardens into a mortar and is turned into plaster by carbon dioxide uptake. Mixed with other compounds, lime forms an important part of Portland cement.

When water percolates through limestone or other soluble carbonate rocks, it partially dissolves part of the rock and causes cave formation and characteristic stalactites and stalagmites and also forms hard water. Other important calcium compounds are nitrate, sulfide, chloride, carbide, cyanamide, and hypochlorite.

Isotopes

Calcium has four stable isotopes (40Ca and 42Ca through 44Ca), plus two more isotopes (46Ca and 48Ca) that have such long half-lives that for all practical purposes they can be considered stable. It also has a cosmogenic isotope, radioactive 41Ca, which has a half-life of 103,000 years. Unlike cosmogenic isotopes that are produced in the atmosphere, 41Ca is produced by neutron activation of **40**Ca. Most of its production is in the upper metre or so of the soil column where the cosmogenic neutron flux is still sufficiently strong. **41**Ca has received much attention in stellar studies because it decays to **41**K, a critical indicator of solar-system anomalies.

97% of naturally occurring calcium is in the form of **40**Ca. **40**Ca is one of the daughter products of **40**K decay, along with **40**Ar. While K-Ar dating has been used extensively in the geological sciences, the prevalence of 40Ca in nature has impeded its use in dating. Techniques using mass spectrometry and a double spike isotope dilution have been used for K-Ca age dating.

Nutrition

Calcium is an important component of a healthy diet. A deficit can affect bone and tooth formation, while overretention can cause kidney stones. Vitamin D is needed to absorb calcium. Dairy products, such as milk and cheese, are a well-known source of calcium. However, some individuals are allergic to dairy products and even more people, particularly those of non-European descent, are lactose-intolerant, leaving them unable to consume dairy products. Fortunately, many other good sources of calcium exist. These include: seaweeds such as kelp, wakame and hijiki; nuts and seeds (like almonds and sesame); beans; amaranth; collard greens; okra; rutabaga; broccoli; kale; and fortified products such as orange juice and soy milk. Calcium has also been found to assist in the production of lymphatic fluids.

Calcium is essential for the normal growth and maintenance of bones and teeth, and calcium requirements must be met throughout life. Requirements are greatest during periods of growth, such as childhood, during pregnancy and when breast-feeding. Long-term calcium deficiency can lead to osteoporosis, in which the bone deteriorates and there is an increased risk of fractures. Adults need between 1,000 and 1,300 mg of calcium in their daily diet.[1]

Recommended Adequate Intake by the IOM for Calcium:[1]

Age------------------------Calcium (mg/day)

0 to 6 months--------------210

7 to 12 months-------------270

1 to 3 years---------------500

4 to 8 years---------------800

9 to 13 years-------------1300

14 to 18 years------------1300

19 to 50 years------------1000

51+ years-----------------1200

For more information about calcium in living nature, see calcium in biology.

Dietary sources of calcium

Calcium is found in significant amounts in many foods, including broccoli, kale, dandelion greens, collard greens, almonds, sesame seeds, blackstrap molasses, beans, and fortified beverages such as soy milk and orange juice. The calcium content of most foods can be found in the USDA National Nutrient Database.[2]

Dairy products (such as milk, yogurt and cheese) do contain calcium, however they are not recommended as a dietary source because they contain a significant amount of saturated fat, which can contribute to cardiovascular disease. The calcium content of dairy products is also misleading because most of the calcium is used by the body in the digestion of milk protein (casein). This can lead to calcium deficiency and osteoporosis.

However, calcium in dairy products is usually absorbed more easily by the human body than the calcium in other sources such as plant based or dietary supplements.

Dietary calcium supplements

Calcium supplements are used to prevent and to treat calcium deficiencies. There are conflicting recommendations about when to take calcium supplements. However, most experts agree that no more than 500 mg should be taken at a time because the percent of calcium absorbed decreases as the amount of calcium in the supplement increases.[1] It is recommended to spread doses throughout the day, with the last dose near bedtime. Recommended daily calcium intake varies from 1000 to 1500 mg, depending upon the stage of life.

In July 2006, a report citing research from Fred Hutchinson Cancer Research Center in Seattle, Washington claimed that women in their 50's gained 5 pounds less in a period of 10 years by taking more than 500 mg of calcium supplements than those who did not. However, the doctor in charge of the study, Dr. Alejandro J. Gonzalez also noted it would be stretching it to suggest calcium supplements as a weight-limiting aid.[3]

- Calcium carbonate is the most common and least expensive calcium supplement. It can be difficult to digest and causes gas in some people. Taking magnesium with it can help to prevent constipation. Calcium carbonate is 40% elemental calcium. 1000 mg will provide 400 mg of calcium. It is recommended to take this supplement with food to aid in absorption. In some calcium supplements based on calcium carbonate, vitamin D is added to aid in absorption. Vitamin D is needed for the absorption of calcium from the stomach and for the functioning of calcium in the body.[4][5]
- Calcium citrate is more easily absorbed (bioavailability is 2.5 times higher than calcium carbonate), easier to digest and less likely to cause constipation and gas than calcium carbonate. It also has a lower risk of contributing to the formation of kidney stones. Calcium citrate is about 21% elemental calcium. 1000 mg will provide 210 mg of calcium. It is more expensive than calcium carbonate and more of it must be taken to get the same amount of calcium.

- Calcium phosphate costs more than calcium carbonate, but less than calcium citrate. It is easily absorbed and is less likely to cause constipation and gas than either.
- Calcium lactate and calcium aspartate are both more easily digested, but more expensive than calcium carbonate

See also

- Calcium in biology

Notes

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Calcium in biology

Calcium plays a vital role in the anatomy, physiology and biochemistry of organisms and of the cell, particularly in signal transduction pathways. The skeleton acts as a major mineral storage site for the element and releases Ca2+ ions into the bloodstream under controlled conditions. Circulating calcium is either in the free, ionized form or bound to blood proteins such as albumin. The hormone secreted by the parathyroid gland, parathyroid hormone, regulates the resorption of Ca**2+** from bone.

Measuring Ca2+ in living tissue

The total amount of Ca**2+** present in a tissue may be measured using atomic absorption spectrometry, in which the tissue is vapourized and combusted. To measure Ca2+ in vivo, a range of fluorescent dyes may be used. These dyes are based on Ca2+-binding molecules such as BAPTA and so care is required in their use, because they may actually buffer the Ca**2+** changes which they are used to measure.

Organs and tissues

Different tissues contain Ca in different concentrations. In vertebrates Ca (mostly calcium phosphate and some calcium sulfate) is the most important (and specific) element of bone and calcified cartilage.

Some invertebrates use calcium compounds for building their exoskeleton (shells and carapaces) or endoskeleton (echinoderm plates and poriferan calcareous spicules). Many protists also make use of calcium.

There are also some plants that accumulate Ca in their tissues, thus making them more firm. Calcium is stored as Ca-oxalate crystals in plastids.

Cell biology

In eukaryotes, Ca^{2+} ions are one of the most widespread second messengers used in signal transduction. They make their entrance into the cytoplasm either from outside the cell through the cell membrane via calcium channels (such as Ca-binding proteins), or from some internal calcium storages.

Ca^{2+} entering the cell plasma causes the specific action of the cell, whatever this action is: secretory cells release vesicles with their secretion, muscle cells contract, synapses release synaptic vesicles and go into processes of synaptic plasticity, etc.

Calcium's function in muscle contraction was found as early as 1882 by Ringer and led the way for further investigations to reveal its role as a messenger about a century later. Because its action is interconnected with cAMP, they are called synarchic messengers. Calcium can bind to several different calcium-modulated proteins such as troponin-C (the first one to be identified) or calmodulin. The ions are stored in the sarcoplasmic reticulum of muscle cells.

The same Ca^{2+} ions can, however, bring damage to cells if there are too many of them (for example in the case of excitotoxicity, or overexcitation of neural circuits, which can occur after brain trauma or stroke). Excesses of calcium within a cell may damage it or even cause it to undergo apoptosis. One cause of hypercalcemia is hyperparathyroidism.

Calcium in plants

Structural roles

Ca^{2+} ions are an essential component of plant cell walls and cell membranes, and are used as cations to balance organic anions in the plant vacuole.[1] The Ca^{2+} concentration of the vacuole may reach millimolar levels. The most striking use of Ca^{2+} ions as a structural element in plants occurs in the marine coccolithophores, which use Ca^{2+} to form the calcium carbonate plates with which they are covered.

Cell signalling

Ca^{2+} ions are usually kept at nanomolar levels in the cytosol of plant cells, and act in a number of signal transduction pathways.

Food sources

The USDA web site has a very complete table of calcium content (in mg) of common foods per common measures (link below).

Calcium amount in foods, 100g:

- vaccine = 116 mg

human milk = 33 mg
milk powder = 909 mg
parmesan (cheese) = 1140 mg
ricotta (skimmed milk cheese) = 90 mg
egg, 1 = 54 mg
molasses = 273 mg
brown sugar = 85 mg
white sugar = 0 mg
honey = 5 mg
flour = 41 mg
wheat germ = 72 mg
beef = 12 mg
horse meat = 10 mg
cod = 11 mg
trout = 19 mg
hazels = 250 mg
almonds = 234 mg
nuts = 99 mg
lentils = 79 mg
Rice, white, long-grain, parboiled, enriched, cooked = 19 mg

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Dietary fiber

Dietary fibres are the indigestible portion of plant foods that move food through the digestive system, absorbing water. Chemically, dietary fiber consists of non-starch polysaccharides and several other plant components such as cellulose, lignin, waxes, chitins, pectins, beta-glucans, inulin and oligosaccharides.

Uses

Soluble and insoluble fibres

Sources of dietary fibrer are usually divided into categories of “insoluble” and “soluble”. Both types are present in all plant foods, with varying degrees of each according to a plant’s characteristics. Insoluble refers to lack of solubility in water, but with passive water-attracting properties that help to increase bulk, soften stools and shorten transit time through the intestinal tract. Soluble indicates a fiber source that would readily dissolve in water.

As will be discussed here, those definitions are too limiting, especially because soluble fiber undergoes active metabolic processing via fermentation that yields end-products with broad, significant health effects.

To conceptualize insoluble and soluble fibers, consider the segments of a plum (or prune) — its thick skin covering a juicy pulp. The plum skin is an example of an insoluble fiber source, whereas soluble fiber sources are inside the pulp. Other sources of insoluble fiber include whole wheat, wheat and corn bran, flax seed lignans and vegetables such as carrots, celery, green beans and potato skins.

One of the most versatile sources of dietary fiber is the husk (hull) of seeds from psyllium grain (Plantago ovata), a fiber source with clinically demonstrated properties of lowering blood cholesterol when chronically included in human diets. Psyllium seed husk is 34% insoluble fiber and 66% soluble fiber, providing an optimal division of both types that make it a valuable food additive.

Fermentable fiber

The American Association of Cereal Chemists defined soluble fiber this way: “the edible parts of plants or similar carbohydrates resistant to digestion and absorption in the human small intestine with complete or partial fermentation in the large intestine”.

There are several key words in that statement that invite analysis and comment for considering fermentable fiber.

edible parts of plants — indicates that all parts of a plant we eat — skin, pulp, seeds, stems, leaves, roots — contain fiber. Both insoluble and soluble sources would be in those plant components.

carbohydrates — complex carbohydrates, such as long-chained sugars also called starch, oligosaccharides or polysaccharides, are excellent sources of fiber.

resistant to digestion and absorption in the human small intestine — foods providing nutrients are digested by enzymes and acids in the stomach and small intestine where the nutrients are released then absorbed through the intestinal wall for transport via the blood throughout the body. A food resistant to this process is undigested, as insoluble and soluble fibers are. They pass to the large intestine only affected by their absorption of water (insoluble fiber) or dissolution in water (soluble fiber).

complete or partial *fermentation* in the large intestine — the large intestine is comprised mainly of a segment called the colon within which additional nutrient absorption occurs

through the process of fermentation. Fermentation occurs by the action of colonic bacteria on the food mass, producing gases and short-chain fatty acids. It is these short-chain fatty acids — butyric, acetic, propionic, and valeric acids — that have such significant health properties.

Short-chain fatty acids

Short-chain fatty acids are used by the intestinal mucosa or absorbed through the colonic wall for portal circulation (supplying the liver) that transports them into the general circulation. Particularly butyric acid has extensive physiological actions that promote health effects among which are:

- Stabilize blood glucose levels by acting on pancreatic insulin release and liver control of glycogen breakdown
- Suppress cholesterol synthesis by the liver and reduce blood levels of low-density lipids (LDL cholesterol) and triglycerides responsible for atherosclerosis
- Lower colonic pH (i.e., raise the acidity levels in the colon) which protects the colon lining from cancer polyp formation and increases absorption of minerals
- Stimulate production of T helper cells, antibodies, leukocytes, splenocyte cytokines and lymph mechanisms having crucial roles in immune protection
- Increase proliferation of colonic bacteria beneficial for intestinal health — bifidobacteria and lactobacilli (serving a probiotic function)
- Improve barrier properties of the colonic mucosal layer, inhibiting inflammatory and adhesion irritants

Summarizing these effects, fermentable fibers yield the important short-chain fatty acids that affect blood glucose and lipid levels, improve the colonic environment and regulate immune responses.

Regulatory guidance on fiber products

On average, North Americans consume less than 50% of the dietary fiber levels required for good health. In the preferred food choices of today's youth, this value may be as low as 20%, a factor considered by experts as contributing to the obesity crisis seen in many first-world western countries.

Recognizing the growing scientific evidence for physiological benefits of increased fiber intake, regulatory agencies such as the US Food and Drug Administration (FDA) have given approvals to food products making health claims for fiber.

In clinical trials to date, these fiber sources were shown to significantly reduce blood cholesterol levels and so are important to cardiovascular health.

Soluble (fermentable) fiber sources gaining FDA approval are

- Psyllium seed husk (7 grams per day)

- Beta-glucan from oat bran, whole oats, oatrim or rolled oats (3 grams per day)
- Beta-glucan from whole grain or dry-milled barley (3 grams per day)

Other examples of fermentable fiber sources (from plant foods or biotechnology) used in functional foods and supplements include inulin, fructans, xanthan gum, cellulose, guar gum, fructooligosaccharides (FOS) and oligo- or polysaccharides.

Consistent intake of fermentable fiber through foods like berries and other fresh fruit, vegetables, whole grains, seeds and nuts is now known to reduce risk of some of the world's most prevalent diseases — obesity, diabetes, high blood cholesterol, cardiovascular disease, and numerous gastrointestinal disorders. In this last category are constipation, inflammatory bowel disease, ulcerative colitis, hemorrhoids, Crohn's disease, diverticulitis and colon cancer — all disorders of the intestinal tract where fermentable fiber can provide healthful benefits.

Although many researchers believe that dietary fiber intake reduces the risk of colon cancer, one study, conducted by researchers at the Harvard School of Medicine of over 88,000 women, did not show a statistically significant relationship between higher fiber consumption and lower rates of colorectal cancer or adenomas.[1]

Guidelines on fiber intake

The American Dietetic Association (ADA) recommends a minimum of 20-35 g/day for a healthy adult depending on calorie intake (e.g., a 2000 cal/8400 kj diet should include 25 g of fiber per day). The ADA's recommendation for a child was that intake should equal age in years plus 5 g/day for children (e.g., a 4 year old should consume 9 g/day). No guidelines have yet been established for the elderly or very ill. Patients with current constipation, vomiting, and abdominal pain should see a physician. Certain bulking agents are not commonly recommended with the prescription of opioids because the slow transit time mixed with larger stools may lead to severe constipation, pain, or obstruction.

The British Nutrition Foundation has recommended a minimum fiber intake of 12-24 g/day for healthy adults.

Sources of fiber

Current recommendations suggest that adults consume 20-35 grams of dietary fiber per day, but the average American's daily intake of dietary fiber is only 14-15 grams. The ADA recommends trying to get most of your dietary fiber from foods you eat, as an important part of consuming variety, nutrition, synergy between nutrients, and possibly phytonutrients. Soluble fiber is found in many foods, including:

- legumes (peas, soybeans, and other beans)

oats, rye, and barley
some fruits (particularly apples, bananas), and berries
certain vegetables, such as broccoli and carrots
root vegetables, such as potatoes and yams (the skins are insoluble fiber)
psyllium seed (only about T soluble fiber).

Legumes also typically contain shorter-chain carbohydrates that are indigestible by the human digestive tract but which are digested by bacteria in the large intestine (colon), which is a cause of flatulence.

Sources of insoluble fiber include

- whole grain foods

bran

nuts and seeds

vegetables such as green beans, cauliflower, zucchini, celery

the skins of some fruits, including tomatoes

Fiber supplements

There are many types of soluble fiber supplements available to consumers for nutritional purposes, for the treatment of various gastrointestinal disorders, and for such possible health benefits as lowering cholesterol levels, reducing the risk of colon cancer, or losing weight. Soluble fiber supplements are particularly beneficial for Irritable Bowel Syndrome symptoms such as diarrhea and/or constipation, and abdominal pain (Van Vorous, 2000). Prebiotic soluble fiber supplements (acacia, FOS, inulin) are a promising area of treatment for inflammatory bowel disease (Seidner, 2005) such as Crohn's disease and ulcerative colitis, and Clostridium difficile (May, 1994), due to the short-chain fatty acids they produce, and subsequent anti-inflammatory actions upon the bowel.

Psyllium husk

Psyllium seed husk (best known under the brand Metamucil). Psyllium husk may reduce the risk of heart disease by lowering cholesterol levels, and is known to help alleviate the symptoms of irritable bowel syndrome, though it often causes uncomfortable bloating. Psyllium husk is often labeled a "bulk-forming laxative", which can be misleading, because it can also help diarrhoea and it does not cause bowel dependency. Konsyl (Konsyl Pharmaceuticals) is another brand.

The FDA allows foods containing 0.75 g of psyllium husk fiber or 1.7 g of oat fiber to claim that they may be able to reduce the risk of heart disease (J Am Diet Assoc 2002).

Methylcellulose

Methylcellulose is created from the cell wall of plants. Sold as a powder, it is undigestible and doesn't have calories that humans can use. Citrucel (by GlaxoSmithKline), and Celevac (Shire) are popular brands of methylcellulose.

Polycarbophil

Vegetable gums

Vegetable gum fiber supplements are relatively new to the market. Often sold as a powder, vegetable gum fibers dissolve easily with no aftertaste. They are effective for the treatment of Irritable Bowel Syndrome (Parisi, 2002)[verification needed]. Examples of vegetable gum fibers are guar gum (brand name Benefiber) and acacia gum (brand name Heather's Tummy Fiber).

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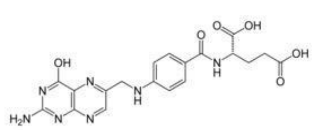
Folic acid



Systematic name

N-[4(2-Amino-4-hydroxy-
pteridin-6-ylmethylamino)-
benzoyl]-L(+)-glutamic acid.

Other names

pteroyl-L-glutamic acid,
Vitamin B9, Vitamin M,
Folacin

Molecular formula $C_{19}H_{19}N_{7}O_{6}$

SMILES

*C1=CC(=CC=C1C(=O)NC
(CCC(=O)O)C(=O)O)
NCC2=CN=C3C(=N2)
C(=O)N=C(N3)N*

Molar mass 441.1396 g/mol

Appearance yellow-orange, crystalline powder

CAS number [59-30-3]

Properties

Solubility in water 8.5 g/100 ml (20 °C)

In ethanol, ether, acetone insoluble

Melting point 250 °C (523 K), decomp.

Acidity (pK_a) 1st: 2.3, 2nd: 8.3

Chiral rotation $[\pm]_D$ +23°
0.5% in 0.1 M NaOH

Hazards

Main hazards non-toxic, non-flammable

R/S statement R: - S: 24/25

RTECS number LP5425000

UV-Vis

Lambda-max (pH 13)

259 nm
368 nm

Extinction coefficient (pH 13)

32340 (259 nm)
7410 (368 nm)

Related compounds

Salts sodium folate

Except where noted otherwise, data are given for materials in their standard state (at 25°C, 100 kPa)

Folic acid and *folate* (the anion form) are forms of a water-soluble B vitamin. These occur naturally in food and can also be taken as supplements. Folate gets its name from the Latin word folium, leaf.

Folate in foods

Leaf vegetables such as spinach and turnip greens, dried beans and peas, fortified cereal products, sun flower seeds and some other fruits and vegetables are rich sources of folate. Some breakfast cereals (ready-to-eat and others) are fortified with 25 percent or 100 percent of the recommended dietary allowance (RDA) for folic acid. A table of selected food sources of folate and folic acid can be found at the USDA National Nutrient Database for Standard Reference.

Recently there have been debates in the United Kingdom [1] and Australasia [2]about including folic acid in products such as bread and flour. Experts claim that this will decrease the number of babies with disabilities such as spina bifida. Research suggests high levels of folic acid can interfere with some antimalarial treatments. [3]

History

A key observation of researcher Lucy Wills in 1931 led to the identification of folate as the nutrient needed to prevent the anemia of pregnancy. Dr. Wills demonstrated that the anemia could be corrected by brewer's yeast. Folate was identified as the corrective substance in brewer's yeast in the late 1930s and was extracted from spinach leaves in 1941. It was synthesised in 1946.

Biological roles

Folate is necessary for the production and maintenance of new cells.[4] This is especially important during periods of rapid cell division and growth such as infancy and pregnancy. Folate is needed to replicate DNA. It also helps prevent changes to DNA that may lead to cancer. Thus folate deficiency hinders DNA synthesis and cell division, affecting most clinically the bone marrow, a site of rapid cell turnover. Because RNA and protein synthesis are not hindered, large red blood cells called megaloblasts are produced, resulting in megaloblastic anemia.[5] Both adults and children need folate to make normal red blood cells and prevent anemia.[6]

Biochemistry

In the form of a series of tetrahydrofolate compounds, folate derivatives are substrates in a number of single-carbon-transfer reactions, and also are involved in the synthesis of dTMP (2'-deoxythymidine-5'-phosphate) from dUMP (2'-deoxyuridine-5'-phosphate). It helps convert vitamin B12 to one of its coenzyme forms and helps synthesize the DNA required for all rapidly growing cells.

The pathway in the formation of tetrahydrofolate (FH***4***) is the reduction of folate (F) to dihydrofolate (FH***2***) and then the subsequent reduction of dihydrofolate to tetrahydrofolate (FH4). Both these sequential reactions are carried out by dihydrofolate reductase EC 1.5.1.3.

Methylene tetrahydrofolate (CH***2***FH***4***) is formed from tetrahydrofolate by the addition of methylene groups from one of three carbon donors: formaldehyde, serine, or glycine. *Methyl tetrahydrofolate* (CH***3***–FH***4***) can be made from methylene tetrahydrofolate by reduction of the methylene group, and *formyl tetrahydrofolate* (CHO-FH***4***, folinic acid) is made by oxidation of methylene tetrahydrofolate.

In other words:

F ’ FH***2*** ’ FH***4*** ’ CH***2***=FH***4*** ’ 1-carbon chemistry

A number of drugs interfere with the biosynthesis of folic acid and tetrahydrofolate. Among them are the dihydrofolate reductase inhibitors (such as trimethoprim and pyrimethamine), the sulfonamides (competitive inhibitors of para-aminobenzoic acid in the reactions of dihydropteroate synthetase), and the anticancer drug methotrexate (inhibits both folate reductase and dihydrofolate reductase).

Recommended Dietary Allowance for folate

The Recommended Dietary Allowance (RDA) is the average daily dietary intake level that is sufficient to meet the nutrient requirements of nearly all (97 to 98 percent) healthy individuals in each life-stage and gender group. The 1998 RDAs for folate are expressed in a term called the Dietary Folate Equivalent (DFE). This was developed to help account for the differences in absorption of naturally-occurring dietary folate and the more bioavailable synthetic folic acid.[7] The 1998 RDAs for folate expressed in micrograms (µg) of DFE for adults are:

1998 RDAs for Folate

Men	Women		
(19+)	(19+)	Pregnancy	Breast feeding
400 µg	400 µg	600 µg	500 µg
1 µg of food folate = 0.6 µg folic acid from supplements and fortified foods			

The National Health and Nutrition Examination Survey (NHANES III 1988-91) and the Continuing Survey of Food Intakes by Individuals (1994-96 CSFII) indicated that most adults did not consume adequate folate.[8][9] However, the folic acid fortification program in the United States has increased folic acid content of commonly eaten foods such as cereals and grains, and as a result diets of most adults now provide recommended amounts of folate equivalents.[10]

Folic acid and pregnancy

Folic acid is very important for all women who may become pregnant. Adequate folate intake during the periconceptional period, the time just before and just after a woman becomes pregnant, helps protect against a number of congenital malformations including neural tube defects.[11] Neural tube defects result in malformations of the spine (spina bifida), skull, and brain (anencephaly). The risk of neural tube defects is significantly reduced when supplemental folic acid is consumed in addition to a healthy diet prior to and during the first month following conception.[12][13] Women who could become pregnant are advised to eat foods fortified with folic acid or take supplements in addition to eating folate-rich foods to reduce the risk of some serious birth defects. Taking 400 micrograms of synthetic folic acid daily from fortified foods and/or supplements has been suggested. The Recommended Dietary Allowance (RDA) for folate equivalents for pregnant women is 600 micrograms.

Folic acid supplements and masking of B*12* deficiency

There has been concern about the interaction between vitamin B12 and folic acid. Folic acid supplements can correct the anemia associated with vitamin B12 deficiency. Unfortunately, folic acid will not correct changes in the nervous system that result from vitamin B12 deficiency. Permanent nerve damage could theoretically occur if vitamin B12 deficiency is not treated. Therefore, intake of supplemental folic acid should not exceed 1000 micrograms (1000 mcg or 1 mg) per day to prevent folic acid from masking symptoms of vitamin B***12*** deficiency. In fact, evidence that such masking actually occurs is scarce, and there is no evidence that folic acid fortification in Canada or the US has increased the prevalence of vitamin B***12*** deficiency or its consequences.

Still it is important for older adults to be aware of the relationship between folic acid and vitamin B***12*** because they are at greater risk of having a vitamin B***12*** deficiency. If you are 50 years of age or older, ask your physician to check your B***12*** status before you take a supplement that contains folic acid.

Health risk of too much folic acid

The risk of toxicity from folic acid is low.[14] The Institute of Medicine has established a tolerable upper intake level (UL) for folate of 1,000 µg for adult men and women, and a UL of 800 µg for pregnant and lactating (breast-feeding) women less than 18 years of age. Supplemental folic acid should not exceed the UL to prevent folic acid from masking symptoms of vitamin B_{12} deficiency.[15]

Some current issues and controversies about folate

Dietary fortification of folic acid

Since the discovery of the link between insufficient folic acid and neural tube defects (NTDs), governments and health organisations worldwide have made recommendations concerning folic acid supplementation for women intending to become pregnant. For example, the United States Public Health Service (see External links) recommends an extra 0.4 mg/day, which can be taken as a pill. However, many researchers believe that supplementation in this way can never work effectively enough since not all pregnancies are planned and not all women will comply with the recommendation.

This has led to the introduction in many countries of fortification, where folic acid is added to flour with the intention of everyone benefiting from the associated rise in blood folate levels. This is not uncontroversial, with issues having been raised concerning individual liberty, and the masking effect of folate fortification on pernicious anaemia (vitamin B12 deficiency). However, most North and South American countries now fortify their flour, along with a number of Middle Eastern countries and Indonesia. Mongolia and a number of ex-Soviet republics are amongst those having widespread voluntary fortification; about five more countries (including Morocco, the first African country) have agreed but not yet implemented fortification. Previously, the UK had decided not to fortify, mainly because of the vitamin B12 concern. However, this decision is currently being reconsidered by the Food Standards Agency. Thus far, no EU country has yet fortified. Australia is considering fortification, but a period for comments ending 31 July 2006 attracted strong opposition from industry as well as academia.[16]

In 1996, the United States Food and Drug Administration (FDA) published regulations requiring the addition of folic acid to enriched breads, cereals, flours, corn meals, pastas, rice, and other grain products.[17][18] This ruling took effect 1998-01-01, and was specifically targeted to reduce the risk of neural tube birth defects in newborns.[19] There are concerns that the amount of folate added is insufficient[2]. In October 2006, the Australian press claimed that U.S. regulations requiring fortification of grain products were being interpreted as disallowing fortification in non-grain products, specifically Vegemite (an Australian yeast extract containing folate). The FDA later said the report was inaccurate, and no ban or other action was being taken against Vegemite.

Since the folic acid fortification program took effect, fortified foods have become a major source of folic acid in the American diet. The Centers for Disease Control and Prevention in Atlanta, Georgia used data from 23 birth defect registries that cover about half of United States births and extrapolated their findings to the rest of the country. This data indicates that since the addition of folic acid in grain-based foods as mandated by the Food and Drug Administration, the rate of neural tube defects dropped by 25 percent in the United States.[20]

Although folic acid does reduce the risk of birth defects, it is only one part of the picture and should not be considered a cure. Even women taking daily folic acid supplements have been known to have children with neural tube defects.

Folic acid and heart disease

Low concentrations of folate, vitamin B***12***, or vitamin B***6*** may increase your level of homocysteine, an amino acid normally found in your blood. There is evidence that an elevated homocysteine level is an independent risk factor for heart disease and stroke.[21] The evidence suggests that high levels of homocysteine may damage coronary arteries or make it easier for blood clotting cells called platelets to clump together and form a clot.[22] However, there is currently no evidence available to suggest that lowering homocysteine with vitamins will reduce your risk of heart disease. Clinical intervention trials are needed to determine whether supplementation with folic acid, vitamin B***12*** or vitamin B***6*** can lower your risk of developing coronary heart disease. The NORVIT trialsuggests that folic acid supplementation may do more harm than good.

As of 2006, studies have shown that giving folic acid to reduce levels of homocysteine does not result in clinical benefit and suggests that in combination with B***12*** may even increase some cardiovascular risks.[23][24][25]

Folic acid and cancer

Some evidence associates low blood levels of folate with a greater risk of cancer.[26] Folate is involved in the synthesis, repair, and functioning of DNA, our genetic map, and a deficiency of folate may result in damage to DNA that may lead to cancer.[27] Several studies have associated diets low in folate with increased risk of breast, pancreatic, and colon cancer.[28] Findings from a study of over 121,000 nurses suggested that long-term folic acid supplementation (for 15 years) was associated with a decreased risk of colon cancer in women 55 to 69 years of age.[29]

"Folate intake counteracts breast cancer risk associated with alcohol consumption" [30] and "women who drink alcohol and have a high folate intake are not at increased risk of cancer" [31]. Those who have a high (200 micrograms or more per day) level of folate (folic acid or Vitamin B9) in their diet are not at increased risk of breast cancer compared to those who abstain from alcohol [32].

However, associations between diet and disease do not indicate a direct cause. Researchers are continuing to investigate whether enhanced folate intake from foods or folic acid supplements may reduce the risk of cancer. Until results from such clinical trials are available, folic acid supplements should not be recommended to reduce the risk of cancer.

Folic acid and methotrexate for cancer

Folate is important for cells and tissues that rapidly divide.[4] Cancer cells divide rapidly, and drugs that interfere with folate metabolism are used to treat cancer. Methotrexate is a drug often used to treat cancer because it inhibits the production of the active form, tetrahydrofolate. Unfortunately, methotrexate can be toxic,[33][34][35] producing side effects such as inflammation in the digestive tract that make it difficult to eat normally.

Folinic acid is a form of folate that can help "rescue" or reverse the toxic effects of methotrexate.[36] Folinic acid is not the same as folic acid. Folic acid supplements have little established role in cancer chemotherapy.[37][38] There have been cases of severe adverse effects of accidental substitution of folic acid for folinic acid in patients receiving methotrexate cancer chemotherapy. It is important for anyone receiving methotrexate to follow medical advice on the use of folic or folinic acid supplements.

Folic acid and methotrexate for non-cancerous diseases

Low dose methotrexate is used to treat a wide variety of non-cancerous diseases such as rheumatoid arthritis, lupus, psoriasis, asthma, sarcoidoisis, primary biliary cirrhosis, and inflammatory bowel disease.[39] Low doses of methotrexate can deplete folate stores and cause side effects that are similar to folate deficiency. Both high folate diets and supplemental folic acid may help reduce the toxic side effects of low dose methotrexate without decreasing its effectiveness.[40][41] Anyone taking low dose methotrexate for the health problems listed above should consult with a physician about the need for a folic acid supplement.

Folic acid and depression

Some evidence links low levels of folate with depression.[42] There is some limited evidence from randomised controlled trials that using folic acid in addition to antidepressant medication may have benefits.[43] However, the evidence is probably too limited at present for this to be a routine treatment recommendation.

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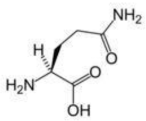
Glutamine



Chemical structure of L-glutamine

Systematic name (2S)-2-amino-4-carbamoyl-butanoic acid

Chemical formula $C_5H_{10}N_2O_3$

Molar mass 146.15 g mol1

Glutamine (Gln) is one of the 20 amino acids encoded by the standard genetic code. Its side chain is an amide; it is formed by replacing a side-chain hydroxyl of glutamic acid with an amine functional group.

Biochemistry

Formation and Nomenclature

Glutamine is genetically coded for by the RNA codons CAA and CAG. Glutamine's three-letter abbreviation is *Gln*, and its one-letter abbreviation is *Q*. A three-letter designation for either glutamine or glutamic acid is *Glx* (one-letter abbreviation: *Z*).

Like other amino acids, glutamine is biochemically important as a constituent of proteins. Glutamine is also crucial in nitrogen metabolism. Ammonia (formed by nitrogen fixation) is assimilated into organic compounds by converting glutamic acid to glutamine. The enzyme that accomplishes this is called glutamine synthetase. Glutamine can, hence, be used as a nitrogen donor in the biosynthesis of many compounds, including other amino acids, purines, and pyrimidines.

Nutrition

Occurrences in Nature

Glutamine is found in foods high in proteins, such as fish, red meat, beans, and dairy products.

Use

Glutamine is a supplement that is used in weightlifting, bodybuilding, endurance and other sports, as well as by those who suffer from muscular cramps or pain—particularly elderly people. It has been shown to speed up the Krebs Cycle, aiding in weight loss while retaining muscle[citation needed]. The main use of glutamine within the diet of either group

is as a means of replenishing the body's stores of amino acids that have been used during exercise or everyday activities.

Studies which are looking into problems with excessive consumption of glutamine thus far have proved inconclusive. However, normal supplementation is healthy mainly because glutamine is supposed to be supplemented after prolonged periods of exercise (for example, a workout or exercise in which amino acids are required for use) and replenishes amino acid stores; this being the main reason glutamine is recommended during fasting or for people who suffer from physical trauma, immune deficiencies, or cancer.[1]

Aiding gastrointestinal function

There have been several recent studies into the effects of glutamine and what properties it possesses, and, there is now a significant body of evidence that links glutamine-enriched diets with intestinal effects; aiding maintenance of gut barrier function, intestinal cell proliferation and differentiation, as well as generally reducing septic morbidity and the symptoms of Irritable Bowel Syndrome. The reason for such "cleansing" properties is thought to stem from the fact that the intestinal extraction rate of glutamine is higher than that for other amino acids, and is therefore thought to be the most viable option when attempting to alleviate conditions relating to the gut. [1]

These conditions were discovered after comparing plasma concentration within the gut between glutamine-enriched and non glutamine-enriched diets. However, even though glutamine is thought to have "cleansing" properties and effects, it is unknown to what extent glutamine has clinical benefits, due to the varied concentrations of glutamine in varieties of food. [1]

Aiding recovery after surgery

It is also known that glutamine has various effects in reducing healing time after operations. Hospital waiting times after abdominal surgery are reduced by providing parenteral nutrition regimens containing amounts of glutamine to patients. Clinical trials have revealed that patients on supplementation regimes containing glutamine have improved nitrogen balances, generation of cysteinyl-leukotrienes from polymorphonuclear neutrophil granulocytes and improved lymphocyte recovery and intestinal permeability (in postoperative patients) - in comparison to those who had no glutamine within their dietary regime; all without any side-effects. [3]

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Linseed oil

Linseed oil is a yellowish drying oil derived from the dried ripe seeds of the flax plant (Linum usitatissimum, Linaceae). It is obtained by pressing, followed by an optional stage of solvent extraction. Cold-pressed oil obtained without solvent extraction is marketed as *flaxseed oil*.

Uses

As a paint binder

Linseed oil is the most commonly used carrier in oil paint. It can also be used as a painting medium, and is available in varieties such as Cold Pressed, Bleached and Refined.

As a wood finish

When used as a wood finish, linseed oil does not cover the surface as varnish does, but soaks into the (visible and microscopic) pores, leaving a shiny but not glossy surface that shows off the grain. Wood treated with linseed oil only is resistant to denting, and scratches are easily repaired, but the wood and oil surface is not as hard as a modern varnish, and it slowly absorbs moisture if allowed to stay wet. Soft wood benefits from the protection from denting but requires more applications and even more drying time than harder wood does, if the grain is to be completely filled. The oil penetrates deeply and fills the grain, because it dries slowly and shrinks little or not at all on hardening. It is a traditional finish for gun stocks, however a very fine finish may require months to obtain. Oiled wood is yellowish and darkens with age.

As a nutritional supplement

Flaxseed oil is suitable for human consumption, and is used as a nutritional supplement. It is rich in omega-3 fatty acids, especially alpha-linolenic acid, which appears to be beneficial for heart disease, inflammatory bowel disease, arthritis and a variety of other health conditions. Flaxseed also contains a group of chemicals called lignans that may play a role in the prevention of cancer.[1]

Additional uses

- Animal feeds

Putty
Sealants
Caulking compounds
Brake linings
Linoleum
Earthen floors
Textiles
Bicycle maintenance as a thread fixative, rust inhibitor and lubricant for the spokes of bicycle wheels
Foundry products
Leather treatment
Polishes, varnishes and oil paints
Animal care products
Wood preservation
Synthetic resins
Treatment for the raw willow wood used to make cricket bats. Linseed oil has a special cultural place in cricket-playing countries.

Boiled linseed oil

Boiled linseed oil is used as a paint binder or as a wood finish on its own. Heating the oil makes it polymerize or oxidise more readily, effectively shortening the drying time. Today most products labeled as "boiled linseed oil" are a combination of raw linseed oil, petroleum-based solvent and metallic dryers. The use of metallic dryers makes boiled linseed oil inedible. There are some products available that contain only heat-treated linseed oil. These are usually labeled as "polymerized" oils though some may still be labeled as boiled.

Nutrient content

Nutrition information from a typical commercially available flaxseed oil:
Per 1 Tbsp (14 g)

- Calories: 130
- Calories from fat:130
- Total fat: 14g
- Omega-3: 8g
- Omega-6: 2g
- Omega-9: 3g

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Erectile dysfunction drugs

Impotence of organic origin

Classifications and external resources

ICD-10

N48.4

ICD-9

607.84

Erectile dysfunction (*ED*) or *impotence* is a sexual dysfunction characterized by the inability to develop or maintain an erection of the penis for satisfactory sexual intercourse regardless of the capability of ejaculation. There are various underlying causes, such as diabetes, many of which are medically reversible.

The causes of erectile dysfunction may be physiological or psychological. Psychological impotence can often be helped by almost anything that the patient believes in; there is a very strong placebo effect.

Due to its embarrassing nature and the shame felt by sufferers, the subject was taboo for a long time, and is the subject of many urban legends. Folk remedies have long been advocated, with some being advertised widely since the 1930s. The introduction of perhaps the first pharmacologically effective remedy for impotence, sildenafil (trade name Viagra), in the 1990s caused a wave of public attention, propelled in part by the news-worthiness of stories about it and heavy advertising.

The Latin term impotentia coeundi describes simple inability to insert the penis into the vagina. It is now mostly replaced by more precise terms.

Medical symptoms

Erectile dysfunction is characterized by the inability to maintain an erection. Normal erections during sleep and in the early morning suggest a psychogenic cause, while loss of these erections may signify underlying disease, often cardiovascular in origin. Other factors leading to erectile dysfunction are diabetes mellitus (causing neuropathy) or hypogonadism (decreased testosterone levels due to disease affecting the testicles or the pituitary gland).

Medical diagnosis

There are no formal tests to diagnose erectile dysfunction. Some blood tests are generally done to exclude underlying disease, such as diabetes, hypogonadism and prolactinoma. Impotence is also related to generally poor physical health, poor dietary habits, obesity, and

most specifically cardiovascular disease such as coronary artery disease and peripheral vascular disease.

A useful and simple way to distinguish between physiological and psychological impotence is to determine whether the patient ever has an erection. If never, the problem is likely to be physiological; if sometimes (however rarely), it is more likely to be psychological. The current diagnostic and statistical manual of mental diseases (DSM-IV) has included a listing for impotence.

Clinical tests used to diagnose ED

Duplex ultrasound Duplex ultrasound is used to evaluate blood flow, venous leak, signs of atherosclerosis, and scarring or calcification of erectile tissue. Injecting prostaglandin, a hormone-like stimulator produced in the body, induces erection. Ultrasound is then used to see vascular dilation and measure penile blood pressure. Measurements are compared to those taken when the penis is flaccid.

Penile nerves function Tests such as the bulbocavernosus reflex test are used to determine if there is sufficient nerve sensation in the penis. The physician squeezes the glans (head) of the penis, which immediately causes the anus to contract if nerve function is normal. A physician measures the latency between squeeze and contraction by observing the anal sphincter or by feeling it with a gloved finger inserted past the anus. Specific nerve tests are used in patients with suspected nerve damage as a result of diabetes or nerve disease.

Nocturnal penile tumescence (NPT) It is normal for a man to have five to six erections during sleep, especially during rapid eye movement (REM). Their absence may indicate a problem with nerve function or blood supply in the penis. There are two methods for measuring changes in penile rigidity and circumference during nocturnal erection: snap gauge and strain gauge.

Penile biothesiometry This test uses electromagnetic vibration to evaluate sensitivity and nerve function in the glans and shaft of the penis. A decreased perception of vibration may indicate nerve damage in the pelvic area, which can lead to impotence.

Penile Angiogram Invasive test - allows visualization of the circulation in the penis and is used during the repair of a priapism.

Dynamic Infusion Cavernosometry (Abbreviated DICC) technique in which fluid is pumped into the penis at a known rate and pressure. It gives a measurement of the vascular pressure in the corpus cavernosum during an erection. To do this test, a vasodilator like prostaglandin E-1 is injected to measure the rate of infusion required to get a rigid erection and to help find how severe the venous leak is.

Corpus Cavernosometry Cavernosography is an adjunct to Dynamic Infusion Cavernosometry, where a contrast material is injected and then it is x-rayed to visualize any leakage.

Digital Subtration Angiography In DSA, the images are acquired digitally. The computer crates a mask from lower-contrast x-rays of the same area and digitally isolates the blood vessels (this is done manually through darkroom masking with traditional angiography).

Magnetic resonance angiography (MRA) This is similar to magnetic resonance imaging. Magnetic resonance angiography uses magnetic fields and radio waves to provide detailed images of the blood vessels. Doctors may inject a "contrast agent" into the patient's

bloodstream that causes vascular tissues to stand out against other tissues. The contrast agent provides for enhanced information regarding blood supply and vascular anomalies. Aside from the IV used to introduce the contrast material into the bloodstream, magnetic resonance angiography is noninvasive and painless.

Pathophysiology

Penile erection is managed by two different mechanisms. The first one is the reflex erection, which is achieved by directly touching the penile shaft. The second is the psychogenic erection, which is achieved by erotic stimuli. The former uses the peripheral nerves and the lower parts of the spinal cord, whereas the latter uses the limbic system of the brain. In both conditions an intact neural system is required for a successful and complete erection. Stimulation of penile shaft by the nervous system leads to the secretion of nitric oxide (NO), which causes the relaxation of smooth muscles of corpora cavernosa (the main erectile tissue of penis), and subsequently penile erection. Additionally, adequate levels of testosterone (produced by the testes) and an intact pituitary gland are required for the development of a healthy male erectile system. As can be understood from the mechanisms of a normal erection, impotence may develop due to hormonal deficiency, disorders of the neural system, lack of adequate penile blood supply or psychological problems. Restriction of blood flow can arise from impaired endothelial function due to the usual causes associated with coronary artery disease, but can also include causation by prolonged exposure to bright light or chronic exposure to high noise levels.

A few causes of impotence may be iatrogenic (medically caused). Various antihypertensives (medications intended to control high blood pressure) and some drugs that modify central nervous system response may inhibit erection by denying blood supply or by altering nerve activity. Antidepressants, especially SSRIs, can cause impotence as a side effect. Surgical intervention for a number of different conditions may remove anatomical structures necessary to erection, damage nerves, or impair blood supply. Some studies have shown that male circumcision may result in an increased risk of impotence,[1][2] while others have found no such effect,[3][4][5] and another found the opposite.[6]

Excessive alcohol use has long been recognised as one cause of impotence, leading to the euphemism "brewer's droop"; Shakespeare made light of this phenomenon in Macbeth.

A study in 2002 found that ED can also be associated with bicycling. The number of hours on a bike and/or the pressure on the penis from the saddle of an upright bicycle is directly related to erectile dysfunction.[7]

Treatment

Treatment depends on the cause. Testosterone supplements may be used for cases due to hormonal deficiency. However, the cause is more usually lack of adequate penile blood supply as a result of damage to inner walls of blood vessels. This damage is more frequent in older men, and often associated with disease, in particular diabetes.

Treatments (with the exception of testosterone supplementation, where effective) work on a temporary basis: they enable an erection to be attained and maintained long enough for intercourse, but do not permanently improve the underlying condition.

ED can in many cases be treated by drugs taken orally, injected, or as penile suppositories. These drugs increase the efficacy of NO, which dilates the blood vessels of corpora cavernosa. When oral drugs or suppositories fail, injections (e.g. of apomorphine) into the erectile tissue of the penile shaft may work.

When pharmacological methods fail, a purpose-designed external vacuum pump can be used to attain erection, with a separate compression ring fitted to the penis to maintain it. These pumps should be distinguished from other "penis pumps" (supplied without compression rings) which, rather than being used for temporary treatment of impotence, are claimed to increase penis length if used frequently, or vibrate as an aid to masturbation.

More drastically, inflatable or rigid penile implants may be fitted surgically. Implants are irreversible and costly.

All these mechanical methods are based on simple principles of hydraulics and mechanics and are quite reliable, but have their disadvantages.

In a few cases there is a vascular problem which can be treated surgically.

Uncontroversial treatments

PDE5 Inhibitors The prescription PDE5 inhibitors sildenafil (Viagra®), vardenafil (Levitra®) and tadalafil (Cialis®) are prescription drugs which are taken orally. They work by blocking the action of PDE5, which causes cGMP to degrade. cGMP causes the smooth muscle of the arteries in the penis to relax, allowing the corpus cavernosum to fill with blood.

Vacuum pump An external vacuum pump will produce an engorged penis with success approaching 90%; a penis ring will maintain this state, although it should be removed after not more than 30 minutes. The erection is not as rigid or hard as a natural erection; drugs or injections, when they work, may be preferable. Various studies show the degree of satisfaction of users and their partners to be vary variable, even when drugs and injections do not work; in one study, about 20% of men who tried a (high-priced) pump decided to proceed to purchase one. Other studies show higher percentages of satisfied users. In some cases frequent use of a vacuum pump can eventually improve the degree of erection attainable without use of the pump. Claims of cheap "penis pumps" to permanently increase maximum penis size should be viewed with caution, however. Some vacuum pumps, such as Osbon ErecAid, are sold at a higher price with 100% refund within 90 days to dissatisfied users, with a somewhat lower price with 50% refund guarantee.[8]This pump is supported by medical insurance schemes, including the UK's NHS and US Medicare and private insurers. The better-known pumps sell for prices of around 200 GBP/400 USD (2006). There is at least one vacuum pump with rings which sells for around one-fifth of this price.[9] (Specific devices are mentioned for information only; mention should not be taken as endorsement).

Inflatable implant
Rigid implant
Surgical treatment of certain cases

Controversial and unapproved treatments

Bremelanotide The experimental drug Bremelanotide (formerly PT-141) does not act on the vascular system like the former compounds but allegedly increases sexual desire and drive in males as well as females. It is applied as a nasal spray. Bremelanotide allegedly works by activating melanocortin receptors in the brain. It is currently in Phase IIb trials.

hMaxi-K hMaxi-K is a form of gene therapy using a plasmid vector that expresses the hSlo gene, that encodes the alpha-subunit of the Maxi-K channel. It has undergone phase I safety trials.[10]

Ginseng A double-blind study appears to show evidence that ginseng is better than placebo: see the ginseng article for more details.

Enzyte Enzyte is a product that has been advertised by saturation coverage on television channels such as CourtTV. However, the Center for Science in the Public Interest (CSPI) has filed a complaint with the Federal Trade Commission (FTC) about Enzyte for deceptive advertising. It is manufactured by Berkeley Nutritionals, which is alleged to be the subject of an investigation by the Attorney General of Ohio and the defendant in class-action lawsuits. Enzyte is a supplement that claims to increase the male libido or frequency of erections of the penis. Commercials for Enzyte are shown regularly on television. These commercials feature a man named Bob who never stops smiling, apparently because he had taken Enzyte and improved the size of his sex organs. The commercials are riddled with symbolic phallic imagery, e.g. golf clubs, remarkably tall glasses of iced tea, and a hose spraying barely a trickle of water (carried by someone who doesn't use Enzyte). The effectiveness of Enzyte is in dispute. Some medical professionals in fact advise against taking Enzyte, saying that it can lead to damage. The Center for Science in the Public Interest have urged the Federal Trade Commission to disallow further television advertising for Enzyte due to a lack of proper studies supporting claims. Enzyte maker Berkeley Premium Nutraceuticals, Inc., is currently under a class action lawsuit for false advertising. Enzyte is said to contain: Tribulus terrestris; Yohimbe Extract; Niacin; Epimedium; Avena sativa; Zinc Oxide; Maca; Muira Pauma; Ginkgo biloba; L-Arginine; Saw Palmetto. Other ingredients: gelatin, rice bran, oat fiber, magnesium stearate, silicon dioxide.

Herbal and other alternative treatments These are generally ineffective when tested blind, but may be useful for their psychological (placebo) effect: if a good result is expected, any highly-praised, and often expensive, treatment can be effective. Reputable drugs can also benefit from the same effect.

Prelox Prelox is a Proprietary mix/combination of naturally occurring ingredients, L-arginine aspartate and Pycnogenol. In double blind tests carried out by Dr. Steven Lamm at New York University School of Medicine, 81.1% of men overall judged Prelox to be effective in improving their ability to engage in sexual activity.Prelox® for improvement of erectile function: A review European Bulletin of Drug Research, Volume 11, No. 3, 2003. Steven Lamm, Frank Schoenlau, Peter Rohdewald Whilst the supplements should be taken daily, the manufacturers claim that it brings the spontaneity back into ones' love life; unlike other products which must be remembered to be taken a fixed time before sexual activity.

History

Dr. John R. Brinkley began a fad for finding cures for male impotence during the 1930s. He used the medium of radio to achieve the same kind of advertising boom to treat the same kind of symptoms.

In the 1930s the American radio airwaves were bombarded with such advertising, first from domestic stations and then upon action by the American Medical Association the media blitz was shifted to superpower Mexican border-blasters.

Surgeons began providing patients with inflatable penile implants in the 1970s.

Modern drug therapy for ED made a significant advance in 1983 when British physiologist Giles Brindley, Ph.D. dropped his trousers and demonstrated to a shocked American Urological Association audience his phentolamine-induced erection. The drug Brindley injected into his penis was a non-specific vasodilator, an alpha-blocking agent, and the mechanism of action was clearly corporal smooth muscle relaxation. The effect that Brindley discovered, established the fundamentals for the later development of specific, safe, orally-effective drug therapies.[11]

Prevalence

The ability to achieve “erection stiffness sufficient for penetration and intercourse” (impotence) decreases with age. Of men aged 50-80 years 30% are impotent. In the age group 70-80 years approximately 50% are unable to achieve erection sufficient for intercourse without treatment (technical support).

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Footnotes

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PDE5 inhibitors

A *phosphodiesterase type 5 inhibitor*, often shortened to *PDE5 inhibitor*, is a drug used to block the degradative action of phosphodiesterase type 5 on cyclic GMP in the smooth muscle cells lining the blood vessels supplying the corpus cavernosum of the penis. These drugs are used in the treatment of erectile dysfunction, and were the first effective oral treatment available for the condition.

Mode of action

Part of the physiological process of erection involves the release of nitric oxide (NO) in vasculature of the corpus cavernosum as a result of sexual stimulation. NO activates the enzyme guanylate cyclase which results in increased levels of cyclic guanosine monophosphate (cGMP), leading to smooth muscle relaxation in blood vessels supplying the corpus cavernosum, resulting in increased inflow of blood and an erection.

PDE5 inhibitors inhibit the degradation of cGMP by phosphodiesterase type 5 (PDE5), increasing bloodflow to the penis during sexual stimulation.

This mode of action means that PDE5 inhibitors are ineffective without sexual stimulation.

Clinical use of PDE5 inhibitors

Indications

PDE5 inhibitors are clinically indicated for the treatment of erectile dysfunction.

Sildenafil, the prototypical PDE5 inhibitor, was originally discovered during the search of a novel treatment for angina. Recent studies are exploring its use as a treatment for pulmonary hypertension (Kanthapillai, Lasserson & Walters, 2004), and its potential for increasing neurogenesis after stroke (Zhang, Wang et. al, 2002).

Contraindications

PDE5 inhibitors are contraindicated in those taking nitrate medication. They are also contraindicated in men for whom sexual intercourse is inadvisable due to cardiovascular risk factors. (Rossi, 2004)

Adverse drug reactions

The occurrence of adverse drug reactions (ADRs) with PDE5 inhibitors appears to be dose related. Headache is a very common ADR, occurring in >10% of patients. Other common ADRs include: dizziness, flushing, dyspepsia, nasal congestion or rhinitis. (Rossi, 2004)

Other ADRs and their incidence vary with the agent and are listed in their individual pages.

Drug interactions

PDE5 inhibitors are primarily metabolised by the cytochrome P450 enzyme CYP3A4. The potential exists for adverse drug interactions with other drugs which inhibit or induce CYP3A4, including HIV protease inhibitors, ketoconazole, itraconazole, etc (Rossi, 2006).

Examples

Sildenafil was the prototypical member of the PDE5 inhibitors. Two other agents, with their own advantages/disadvantages are also available.

- sildenafil
    - tadalafil

  vardenafil

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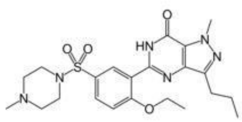
Sildenafil (Viagra)



Systematic (IUPAC) name

1-[4-ethoxy-3-(6,7-dihydro-1-methyl-7-oxo-3-propyl-1H-pyrazolo[4,3-d]pyrimidin-5-yl) phenylsulfonyl]-4-methylpiperazine citrate

Identifiers

CAS number 171599-83-0

ATC code G04**BE03**

PubChem 5281023

DrugBank APRD00556

Chemical data

Formula $C_{22}H_{30}N_6O_4S \cdot C_6H_8O_7$

Mol. weight base: 474.6 g/mol, salt: 666.7 g/mol

SMILES

O=S(=O)(N1CCN(C)CC1)c4cc(C=2NC(=O) c3n(C)nc(CCC)c3N=2)c(OCC)cc4

Pharmacokinetic data

Half life 3-4h

Therapeutic considerations

Pregnancy cat. N/A

Legal status Rx only/POM

Routes Oral

Sildenafil citrate, sold under the names *Viagra*, *Revatio* and generically under various other names, is a drug used to treat male erectile dysfunction (impotence) and pulmonary arterial hypertension (PAH), developed by the pharmaceutical company Pfizer. Viagra pills are blue and diamond-shaped with the words "Pfizer" on one side, and "VGR xx" (where xx stands for "25", "50" or "100", the dose of that pill in milligrams) on the other. Its primary competitors on the market are tadalafil (Cialis), and vardenafil (Levitra).

History

Sildenafil (compound UK-92,480) was synthesized by a group of pharmaceutical chemists working at Pfizer's Sandwich, Kent research facility. It was initially studied for use in hypertension (high blood pressure) and angina pectoris (a form of ischaemic cardiovascular disease). Phase I clinical trials under the direction of Ian Osterloh suggested that the drug had little effect on angina, but that it could induce marked penile erections.[1][2] Pfizer therefore decided to market it for erectile dysfunction, rather than for angina. The drug was patented in 1996, approved for use in erectile dysfunction by the Food and Drug Administration on March 27, 1998, becoming the first pill approved to treat erectile dysfunction in the United States, and offered for sale in the United States later that year.[3] It soon became a great success: annual sales of Viagra in the period 1999–2001 exceeded $1 billion.

The British press portrayed Peter Dunn and Albert Wood as the inventors of the drug, a claim which Pfizer disputes.[4] Their names are on the manufacturing patent application drug, but Pfizer claims this is only for convenience.

Even though sildenafil is only available by prescription from a doctor, it was advertised directly to consumers on US TV (famously being endorsed by Bob Dole). Numerous sites on the Internet offer Viagra for sale after an "online consultation", a mere web questionnaire. The "Viagra" name has become so well known that many fake aphrodisiacs now call themselves "herbal Viagra" or are presented as blue tablets imitating the shape and colour of Pfizer's product. Viagra is also informally known as "Vitamin V", "the Blue Pill", as well as various other nicknames.

Pfizer's worldwide patents on sildenafil citrate will expire in 2011–2013. The UK patent held by Pfizer on the use of PDE5 inhibitors (see below) as treatment of impotence was invalidated in 2000 because of obviousness; this decision was upheld on appeal in 2002.

Mechanism of action

Part of the physiological process of erection involves the parasympathetic nervous system causing the release of nitric oxide (NO) in the corpus cavernosum of the penis. NO binds to the receptors of the enzyme guanylate cyclase which results in increased levels of cyclic guanosine monophosphate (cGMP), leading to smooth muscle relaxation (vasodilation) in the corpus cavernosum, resulting in increased inflow of blood and an erection.

Sildenafil is a potent and selective inhibitor of cGMP specific phosphodiesterase type 5 (PDE5) which is responsible for degradation of cGMP in the corpus cavernosum. The molecular structure of sildenafil is similar to that of cGMP and acts as a competitive binding agent of PDE5 in the corpus cavernosum, resulting in more cGMP and better erections. Without sexual stimulation, and therefore lack of activation of the NO/cGMP system, sildenafil should not cause an erection. Other drugs that operate by the same mechanism include tadalafil (Cialis®) and vardenafil (Levitra®).

Sildenafil is metabolised by hepatic enzymes and excreted by both the liver and kidneys. If taken with a high fat meal, there may be a delay in absorption of sildenafil and the peak effect might be reduced slightly as the plasma concentration will be lowered.

Dosage and price

As with all prescription drugs, proper dosage is at the discretion of a licensed medical doctor. The dose of sildenafil is 25 mg to 100 mg taken once per day between 30 minutes to 4 hours before sexual intercourse.

It is usually recommended to start with a dosage of 50 mg and then lower or raise the dosage as appropriate. The drug is sold in three dosages (25, 50, and 100 mg), all three costing about US$10 per pill. Sildenafil is not scored and it is not advisable to cut it to change dosage since the active compound is not distributed homogenously in the tablet.

Contraindications

Contraindications include:

- When taking nitric oxide donors, organic nitrites and nitrates, such as glyceryl trinitrate, sodium nitroprusside, amyl nitrite ("poppers")[5]
- In men for whom sexual intercourse is inadvisable due to cardiovascular risk factors
- Severe hepatic impairment (decreased liver function)
- Severe impairment in renal function
- Hypotension (low blood pressure)
- Recent stroke or heart attack
- Hereditary degenerative retinal disorders (including genetic disorders of retinal phosphodiesterases)

Side effects

Amongst sildenafil's serious adverse effects are: priapism, severe hypotension, myocardial infarction, ventricular arrhythmias, sudden death, stroke and increased intraocular pressure.

Common side effects include sneezing, headache, flushing, dyspepsia, prolonged erections, palpitations and photophobia. Visual changes including blurring of vision and a curious bluish tinge have also been reported.

Care should be exercised by patients who are also taking Protease inhibitors for the treatment of HIV. Protease inhibitors inhibit the metabolism of sildenafil, effectively multiplying the plasma levels of sildenafil, increasing the incidence and severity of side-effects. It is recommended that patients using protease inhibitors limit their use of sildenafil to no more than one 25-mg dose every 48 hours.

Some sildenafil users have complained of blurriness and loss of peripheral vision. In May of 2005, the U.S. Food and Drug Administration found that sildenafil could lead to vision impairment[6] and a number of studies have linked sildenafil use with nonarteritic anterior ischemic optic neuropathy.[7][8][9][10][11][12]

When used with an alpha blocker, take them at least four hours apart to avoid hypotension.[13]

Other uses

Pulmonary hypertension

As well as erectile dysfunction, sildenafil citrate is also effective in the rare disease pulmonary arterial hypertension (PAH). It relaxes the arterial wall, leading to decreased pulmonary arterial resistance and pressure. This in turn reduces the workload of the right atrium of the heart and improves symptoms of right-sided heart failure. Because PDE-5 is primarily distributed within the arterial wall smooth muscle of the lungs and penis, sildenafil acts selectively in both these areas without inducing vasodilation in other areas of the body. Pfizer submitted an additional registration for sildenafil to the FDA, and sildenafil was approved for this indication in June 2005. The preparation is named Revatio, to avoid confusion with Viagra, and the 20 milligram tablets are white and round. Sildenafil joins bosentan and prostacyclin-based therapies for this condition.[14]

Raynaud's phenomenon

In 2005, Dr. Roland Fries and colleagues reported that sildenafil cut the frequency of Raynaud's phenomenon attacks, reduced their duration by roughly one half, and more than quadrupled the mean capillary blood velocity. This was a double-blind, placebo-controlled crossover trial and the patients had both the primary and secondary forms and had all discontinued the more conventional treatments for this.[15]

Drug abuses

Aphrodisiac

Sildenafil is commonly and increasingly used as an aphrodisiac. While there is no clinical evidence that it has aphrodisiac activity, many seem to believe it will improve sexual performance as well as erectile function and enhance the sexual experience that will occur

Recreational use

Viagra's popularity with young adults has increased over the years.[16] It is sometimes used recreationally. Some users mix Viagra with methylenedioxymethamphetamine (MDMA, ecstasy), a combination known as Sextasy.

Chemical Synthesis

The preparation steps for synthesis of Viagra (sildenafil citrate) are as follows:

1. Methylation of 3-propylpyrazole-5-carboxylic acid ethyl ester with hot dimethyl sulfate.
2. Hydrolysis with aqueous NaOH to free acid.
3. Nitration with oleum/fuming nitric acid.
4. Carboxamide formation with refluxing thionyl chloride/NH4OH.
5. Reduction of nitro group to amino.
6. Acylation with 2-ethoxybenzoyl chloride.
7. Cyclization.
8. Sulfonation to the chlorosulfonyl derivative.
9. Condensation with 1-methylpiperazine.[17]

Notes

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Testosterone

Systematic (IUPAC) name

17b-hydroxy-4-androsten-3-one

Identifiers

CAS number 58-22-0

ATC code G03**BA03**

PubChem 6013

Chemical data

Formula $C_{19}H_{28}O_2$

Mol. weight 288.43

Physical data

Melt. point 155-156 °C (-94 °F)

Spec. rot +110,2°

SEC Combust 11080 kJ/mol

Pharmacokinetic data

Metabolism Liver, Testis and Prostate

Half life 1-12 days

Excretion Urine

Therapeutic considerations

Pregnancy cat. X (USA), Teratogenic effects

Legal status

Schedule III (USA)
Schedule IV (Canada)

Routes Intramuscular injection, transdermal (cream, gel, or patch), oral, sub-'Q' pellet

Testosterone is a steroid hormone from the androgen group. Testosterone is primarily secreted in the testes of males and the ovaries of females although small amounts are secreted by the adrenal glands. It is the principal male sex hormone and an anabolic steroid. In both males and females, it plays key roles in health and well-being. Examples include

enhanced libido, energy, immune function, and protection against osteoporosis. On average, the adult male body produces about twenty times the amount of testosterone that an adult female's body does[1].

Sources of testosterone

Like other steroid hormones, testosterone is derived from cholesterol. The largest amounts of testosterone are produced by the testes in men, but it is also synthesized in smaller quantities in women by the thecal cells of the ovaries, by the placenta, as well as by the zona reticularis of the adrenal cortex in both sexes.

In the testes, testosterone is produced by the Leydig cells. The male generative glands also contain Sertoli cells which require testosterone for spermatogenesis. Like most hormones, testosterone is supplied to target tissues in the blood where much of it is transported bound to a specific plasma protein, *sex hormone binding globulin* (SHBG).

Some drugs specifically target testosterone as a way of treating certain conditions. For example, finasteride inhibits the conversion of testosterone into dihydrotestosterone (DHT), a metabolite which is more potent than testosterone. By lowering the levels of dihydrotestosterone, finasteride may be used for various conditions associated with androgens, such as benign prostatic hyperplasia (BPH) and androgenetic alopecia (male-pattern baldness).

Mechanism of effects

The effects of testosterone in humans and other vertebrates occur by way of two main mechanisms: by activation of the androgen receptor (directly or as DHT), and by conversion to estradiol and activation of certain estrogen receptors.

Free testosterone (T) is transported into the cytoplasm of target tissue cells, where it can bind to the androgen receptor, or can be reduced to 5±-dihydrotestosterone (DHT) by the cytoplasmic enzyme 5±-reductase(5-alfa-reduktas). DHT binds to the same androgen receptor even more strongly than T, so that its androgenic potency is about 2.5 times that of T. The T-receptor or DHT-receptor complex undergoes a structural change that allows it to move into the cell nucleus and bind directly to specific nucleotide sequences of the chromosomal DNA. The areas of binding are called hormone response elements (HREs), and influence transcriptional activity of certain genes, producing the androgen effects. It is important to note that if there is a too low amount of 5±-reductase(5-alfa-reduktas), the body (of a human) will -continue- growing into a female with testicles.

Androgen receptors occur in many different vertebrate body system tissues, and both males and females respond similarly to similar levels. Greatly differing amounts of testosterone prenatally, at puberty, and throughout life account for a large share of biological differences between males and females.

The bones and the brain are two important tissues in humans where the primary effect of testosterone is by way of aromatization to estradiol. In the bones, estradiol accelerates maturation of cartilage into bone, leading to closure of the epiphyses and conclusion of growth. In the central nervous system, testosterone is aromatized to estradiol. Estradiol rather than testosterone serves as the most important feedback signal to the hypothalamus

(especially affecting LH secretion). In many mammals, prenatal or perinatal "masculinization" of the sexually dimorphic areas of the brain by estradiol derived from testosterone programs later male sexual behavior.

Testerone is a predominantly male hormone, though females do produce certain amounts of it. The primary female hormone is estrogen and males also produce certain amounts of this hormone. Testosterone causes the appearance of male traits (i.e deepening voice, pubic and facial hairs, muscular build, etc.)

Effects of testosterone on humans

In general, androgens promote protein synthesis and growth of those tissues with androgen receptors. Testosterone effects can be classified as virilizing and anabolic effects, although the distinction is somewhat artificial, as many of the effects can be considered both. Anabolic effects include growth of muscle mass and strength, increased bone density and strength, and stimulation of linear growth and bone maturation. Virilizing effects include maturation of the sex organs, particularly the penis and the formation of the scrotum in fetuses, and after birth (usually at puberty) a deepening of the voice, growth of the beard and axillary hair. Many of these fall into the category of male secondary sex characteristics.

Testosterone effects can also be classified by the age of usual occurrence. For postnatal effects in both males and females, these are mostly dependent on the levels and duration of circulating free testosterone.

Most of the prenatal androgen effects occur between 7 and 12 weeks of gestation.

- Genital virilization (midline fusion, phallic urethra, scrotal thinning and rugation, phallic enlargement)
- Development of prostate and seminal vesicles

Early infancy androgen effects are the least understood. In the first weeks of life for male infants, testosterone levels rise. The levels remain in a pubertal range for a few months, but usually reach the barely detectable levels of childhood by 4-6 months of age. The function of this rise in humans is unknown. It has been speculated that "brain masculinization" is occurring since no significant changes have been identified in other parts of the body.

Early postnatal effects are the first visible effects of rising androgen levels in childhood, and occur in both boys and girls in puberty.

- Adult-type body odour
- Increased oiliness of skin and hair, acne
- Pubarche (appearance of pubic hair)
- Axillary hair
- Growth spurt, accelerated bone maturation
- Fine upper lip and sideburn hair

Advanced postnatal effects begin to occur when androgen has been higher than normal adult female levels for months or years. In males these are normal late pubertal effects, and only occur in women after prolonged periods of excessive levels of free testosterone in the blood.

- Phallic enlargement (including clitoromegaly)

- Increased libido and erection frequency
- Pubic hair extends to thighs and up toward umbilicus
- Facial hair (sideburns, beard, moustache)
- Chest hair, periareolar hair, perianal hair
- Subcutaneous fat in face decreases
- Increased muscle strength and mass
- Deepening of voice
- Growth of the adam's apple
- Growth of spermatogenic tissue in testes, male fertility
- Growth of jaw, brow, chin, nose, and remodeling of facial bone contours
- Shoulders widen and rib cage expands
- Completion of bone maturation and termination of growth. This occurs indirectly via estradiol metabolites and hence more gradually in men than women.

Adult testosterone effects are more clearly demonstrable in males than in females, but are likely important to both sexes. Some of these effects may decline as testosterone levels decline in the later decades of adult life.

- Maintenance of muscle mass and strength
- Maintenance of bone density and strength
- Libido and erection frequency
- Mental and physical energy

Effects of testosterone on the human brain

As testosterone affects the entire body (often by enlargening, such accepted facts such as, men have bigger hearts, lungs, liver etc) the brain is also affected by this "sexual" advancement, the enzyme aromatase converts testosterone into estrogen that is responsible for "masculinization" of the brain in a male fetus. Factors that in any way reduce this key enzyme(aromatase) can result in an individual with male gender, male body but with a "female" brain. There are some differences in a male and female brain (the result of testosterone) a clear difference is the size, the male human brain is on average larger, however in females the (that do not use testosterone as much) the corpus callosum is proportionally larger in females then males. This means that the effect of testosterone is a greater brain volume, however less interwoven brain halves. [2]

Testosterone in athletes

Testosterone may be administered to an athlete in order to improve performance, and is considered to be a form of doping in most sports. There are several application methods for testosterone, including intramuscular injections, transdermal gels and patches, and implantable pellets.

Anabolic steroids (of which testosterone is one) have also been taken to enhance muscle development, strength, or endurance. After a series of scandals and publicity in the 1980s (such as Ben Johnson's improved performance at the 1988 Summer Olympics), prohibitions

of anabolic steroid use were renewed or strengthened by many sports organizations. Testosterone and other anabolic steroids were designated a "controlled substance" by the United States Congress in 1990, with the Anabolic Steroid Control Act.

Therapeutic use of testosterone

Testosterone was first isolated from a bull in 1935. There have been many pharmaceutical forms over the years. Forms of testosterone for human administration currently available in North America include injectable (such as testosterone cypionate or testosterone enanthate in oil), oral Andriol, buccal Striant, transdermal skin patches, and transdermal creams or gels Androgel and Testim. In the pipeline are a "roll on" delivery method and a nasal spray.

The original and primary use of testosterone is for the treatment of males who have too little or no natural endogenous testosterone production; males with hypogonadism. Appropriate use for this purpose is legitimate hormone replacement therapy, which maintains serum testosterone levels in the normal range.

However, over the years, as with every hormone, testosterone or other anabolic steroids has also been given for many other conditions and purposes besides replacement, with variable success but higher rates of side effects or problems. Examples include infertility, lack of libido or erectile dysfunction, osteoporosis, penile enlargement, height growth, bone marrow stimulation and reversal of anemia, and even appetite stimulation. By the late 1940s testosterone was being touted as an anti-aging wonder drug (e.g., see Paul de Kruif's The Male Hormone).

To take advantage of its virilizing effects, testosterone is often administered to transmen (female-to-male transsexual and transgender people) as part of the hormone replacement therapy, with a "target level" of the normal male testosterone level. And like-wise, transwomen are sometimes prescribed drugs [anti-androgens] to decrease the level of testosterone in the body and allow for the effects of estrogen to develop.

There is a myth that exogenous testosterone can more or less definitively be used for male birth control. However, the vast majority of physicians will agree that to prescribe exogenous testosterone for this purpose is inappropriate. But perhaps more importantly, many men of first hand found this myth to be untrue or at least, unreliable. This is especially true when exogenous testosterone is used in conjunction with hCG.

Exogenous testosterone supplementation comes with a number of health risks. Fluoxymesterone and methyltestosterone are synthetic derivatives of testosterone. In 2006 it was reported that women taking Estratest, a combination pill including estrogen and methyltestosterone, were at considerably heightened risk of breast cancer.

The "testosterone deficiency" of aging and the andropause controversy

Testosterone levels decline gradually with age in men. The clinical significance of this decrease is debated. There is disagreement about if and when to treat aging men with testosterone replacement therapy. The American Society of Andrology's position is that testosterone therapy "is indicated when both clinical symptoms and signs suggestive of androgen deficiency and decreased testosterone levels are present". The American Association of Clinical Endocrinologists says "Hypogonadism is defined as a free testosterone level that is below the lower limit of normal for young adult control subjects. Previously, age-related decreases in free testosterone were once accepted as normal.

Currently, they are not considered normal....Patients with low-normal to subnormal range testosterone levels warrant a clinical trial of testosterone."

There isn't total agreement on the threshold of testosterone value below which a man would be considered hypogonadal. Testosterone can be measured as "free" (that is, bioavailable and unbound) or more commonly, "total" (including the percentage which is chemically bound and unavailable). In the United States, male total testosterone levels below 200 to 300 ng/dl from a morning sample are generally considered low. However these numbers are typically not age-adjusted, but based on an average of a test group which includes elderly males with low testosterone levels. Therefore a value of 300 ng/dl might be normal for a 90 year old male, but not normal for a 30 year old. Identification of inadequate testosterone in an aging male by symptoms alone can be difficult. The signs and symptoms are non-specific, and might be confused with normal aging characteristics, such as loss of muscle mass and bone density, decreased physical endurance, decreased memory ability and loss of libido.

Replacement therapy can take the form of injectable depots, transdermal patches and gels, subcutaneous pellets and oral therapy. Adverse effects of testosterone supplementation include minor side effects such as acne and oily skin, and more significant complications such as increased hematocrit, exacerbation of sleep apnea and acceleration of pre-existing prostate cancer growth. Exogenous testosterone also causes suppression of spermatogenesis and can lead to infertility.[3] It is recommended that physicians screen for prostate cancer with a digital rectal exam and PSA (prostate specific antigen) level prior to initiating therapy, and monitor hematocrit and PSA levels closely during therapy.

Large scale trials to assess the efficiency and long-term safety of testosterone are still lacking. Many caution against embracing testosterone replacement therapy because of lessons from the female hormone replacement therapy trials, where initially promising results were later refuted by larger studies.

Synthesis

Testosterone is synthesized from pregnenolone, which is the precursor of all steroid hormones and is made from cholesterol by a series of enzymatic reactions. Two pathways are possible, In the delta-5 pathway, pregnenolone is converted to DHEA to androstenedione.

In the delta-4 pathway there is hydroxylation of C-17 of progesterone, to yield 17±-hydroxyprogesterone. The side chain is then cleaved to form androstenedione. Androstenedione is the immediate precursor to testosterone.

The keto group on C-17 is reduced to an alcohol to yield testosterone. Testosterone is a potential precursor of estradiol.

Zinc supplementation is known to result in increased levels of testosterone synthesis, especially in those who are zinc deficient. Zinc is critical to the proper function of steroid receptors (see zinc finger) and plays a vital role as a cofactor to many enzymes which is the likely mechanism for its effect on testosterone synthesis.

Notes

1. ^ Williams textbook of endocrinology, Jean D. Wilson pp. 535, 887
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Expectorants

A *mucolytic agent* is any agent which dissolves thick mucus to help relieve respiratory difficulties. (hydrolyzing glycosaminoglycans: tending to break down/lower the viscosity of mucin-containing body secretions/components). The viscosity of mucous secretions in the lungs is dependent upon the concentrations of mucoprotein, the presence of disulfide bonds between these macromolecules and DNA.

Mucolytics: N-acetylcysteine: an aerosolized mucolytic agent often used as adjunctive therapy for pulmonary complications of cystic fibrosis (CF) in combination with vigorous chest physiotherapy. N-acetylcysteine acts to split the sulfide bonds in the macromolecules thereby decreasing viscosity, allowing for removal by normal chest physiology. The action of N-acetylcysteine is pH dependent. Mucolytic action is significant at ranges of pH 7-9.(1)

Natural Mucolytics:

- Mugwort

Non-Mucolytics:

- Guaifenesin: increases volume and decreases viscosity of respiratory tract secretions. (Robitussin)

Potassium iodide

Systematic name Potassium iodide

Other names Kalium iodide, knollide, potide

Molecular formula KI

Molar mass 166.00 g/mol

Appearance white crystalline solid

CAS number [7681-11-0]

Properties

Density and phase 3.13 g/cm3, solid

Solubility in water 128 g/100 ml (6 °C)

Melting point 681 °C (954 K)

Boiling point 1330 °C (1600 K)

Hazards

MSDS External MSDS

Main hazards Slightly hazardous
R/S statement R: 36, 38, 42-43, 61 S: 26, 36-37, 39, 45

RTECS number TT2975000

Related compounds

Other anions potassium bromide, potassium chloride

Other cations lithium iodide, sodium iodide, rubidium iodide, caesium iodid

Except where noted otherwise, data are given for materials in their standard state (at 25 °C, 100 kPa)

Potassium iodide is a white crystalline salt with chemical formula KI, used in photography and radiation treatment. It finds widespread application as an iodide source because it is less hygroscopic than sodium iodide, making it easier to work with. KI can turn yellow upon heating in air or upon standing in moist air for long periods, because of oxidation of the iodide to iodine.

Chemical properties

Potassium iodide behaves as a simple ionic salt, K+I. Since the iodide ion is a mild reducing agent, I is easily oxidised to I2 by powerful oxidising agents such as chlorine:

2 KI(aq) + Cl2(aq) ’ 2 KCl + I2(aq)

Even air will oxidize iodide as evidenced by the observation of a purple extract when KI is rinsed with dichloromethane. Under acidic conditions, KI is oxidised even more easily, due to the formation of hydroiodic acid (HI), which is a powerful reducing agent.

KI forms I***3*** when combined with elemental iodine.

KI(aq) + I2(s) ’ KI3(aq)

Unlike I***2***, I***3*** salts can be highly water-soluble. I***2*** and I***3*** have virtually identical redox potentials (0.535 and 0.536 V vs NHE, respectively), i.e. they are both mild oxidants relative to H***2***. Therefore, this reaction allows the iodine to be used in aqueous solutions for redox titrations.

Potassium iodide also serves in some organic reactions as a source of iodide ion (see "uses" below).

Preparation

Potassium iodide may be prepared by the reaction of a potassium base with hydroiodic acid, for example:

HI + KHCO3 ’ KI + H2O(l) + CO2(g)

Alternatively iron(II) iodide, prepared using scrap iron and iodine (made from iodide rich brines or from Chile saltpeter, can be treated with potassium carbonate:

FeI2 + K2CO3 ’ 2 KI + FeCO3

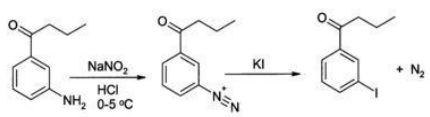
Uses

Potassium iodide is used in photography, in the preparation of silver(I) iodide for high speed photographic film:

KI(aq) + AgNO3(aq) ’ AgI(s) + KNO3(aq)

Potassium iodide is also added to table salt in small quantities to make it "iodized". In a saturated solution, it is also used as an expectorant to treat lung congestion.

KI is often used as a source of iodide ion in organic synthesis. A useful application is in the preparation of aryl iodides from arenediazonium salts[5], for example:



Saturated solution of potassium iodide is also used as treatment for sporotrichosis, a fungal infection.

In medical use, it can also serve as an antiseptic for people suffering from sore throat. The dose is 0.5g-1.0g in 100mL, with the accompany of iodine (0.5g-1.0g in 100mL).

Role of potassium iodide in radiological emergency preparedness

Potassium iodide may also be used to protect the thyroid from radioactive iodine in the event of an accident or attack at a nuclear power plant, or other nuclear attack, especially where a nuclear reactor is breached and the volatile radionuclides, which contain significant amount of 131I, are released into the environment. Radioiodine is a particularly dangerous radionuclide because the body concentrates it in the thyroid gland. Potassium iodide cannot protect against other causes of radiation poisoning, however, nor can it provide any degree of protection against a dirty bomb unless the bomb happens to contain a significant amount of radioactive iodine. In case of a nuclear emergency, iodine used for the cleaning of wounds should *not* be ingested. It is a poison.

Recommended Dosage for Radiological Emergencies involving radioactive iodine [6]

Age = KI in mg = KIO3 in mg

Over 12 years old = 130 = 170

3 - 12 years old = 65 = 85

1 - 36 months old = 32 = 42

< 1 month old = 16 = 21

Precautions

Mild irritant, wear gloves. Chronic overexposure can have adverse effects on the thyroid.

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Gastrointestinal system drugs

The *gastrointestinal tract* or *digestive tract*, also referred to as the *GI tract* or the *alimentary canal*, (nourishment canal) or the *gut*, is the system of organs within multicellular animals which takes in food, digests it to extract energy and nutrients, and expels the remaining waste. This process is called digestion.

The GI tract differs substantially from animal to animal. For instance, some animals have multi-chambered stomachs.

Basic anatomy

The gut

In a normal human adult male, the GI tract is approximately 7.5 meters long (25 feet) and consists of the following components:

Upper gastrointestinal tract

Mouth, Muccal cavity; includes salivary glands, mucosa, teeth and tongue Pharynx Oesophagus or Esophagus (gullet) and cardia Stomach which includes the antrum and pylorus and pyloric sphincter.

Lower gastrointestinal tract

- Bowel or intestine:
  - small intestine, which has three parts:
    - duodenum

jejunum
ileum
  - large intestine, which has three parts:
    - caecum (the vermiform appendix is attached to the cecum).

colon (ascending colon, transverse colon, descending colon and sigmoid flexure)
rectum
- anus

Related organs

The liver secretes bile into the small intestine via the biliary system, employing the gallbladder as a reservoir. The pancreas secretes an isosmotic fluid containing bicarbonate and several enzymes, including trypsin, chymotrypsin, lipase, and pancreatic amylase, as

well as nucleolytic enzymes (deoxyribonuclease and ribonuclease), into the small intestine. Both these secretory organs aid in digestion.

Physiology

Specialization of organs

Four organs are subject to specialization in the kingdom Animalia.

- The first organ is the tongue which is only present in the phylum Chordata.
- The second organ is the esophagus. The crop is an enlargement of the esophagus in birds, insects and other invertebrates that is used to store food temporarily.
- The third organ is the stomach. In addition to a glandular stomach (proventriculus), birds have a muscular "stomach" called the ventriculus or "gizzard." The gizzard is used to mechanically grind up food.
- The fourth organ is the large intestine. An outpouching of the large intestine called the cecum is present in non-ruminant herbivores such as rabbits. It aids in digestion of plant material such as cellulose.

Immune function

The gastrointestinal tract is also a prominent part of the immune system (Coico et al 2003). The low pH (ranging from 1 to 4) of the stomach is fatal for many microorganisms that enter it. Similarly, mucus (containing IgA antibodies) neutralizes many of these microorganisms. Other factors in the GI tract help with immune function as well, including enzymes in the saliva and bile. Health enhancing intestinal bacteria serve to prevent the overgrowth of potentially harmful bacteria in the gut.

Histology

The GI tract has a uniform general histology with some differences which reflect the specialization in functional anatomy. The GI tract can be divided into 4 concentric layers:

- mucosa

submucosa
muscularis externa (the external muscle layer)
adventitia or serosa

Mucosa

The mucosa is the innermost layer of the GI tract, surrounding the lumen, or space within the tube. This layer comes in direct contact with the food (or bolus), and is responsible for absorption and secretion, important processes in digestion.

The mucosa can be divided into:

- epithelium

lamina propria
muscularis mucosae

The mucosa are highly specialized in each organ of the GI tract, facing a low pH in the stomach, absorbing a multitude of different substances in the small intestine, and also absorbing specific quantities of water in the large intestine. Reflecting the varying needs of these organs, the structure of the mucosa can consist of invaginations of secretory glands (i.e. gastric pits), or it can be folded in order to increase surface area (i.e. villi, microvilli).

Submucosa

The submucosa consists of a dense irregular layer of connective tissue with large blood vessels, lymphatics and nerves branching into the mucosa and muscularis. It contains Meissner's plexus, an enteric nervous plexa, situated on the inner surface of the muscularis externa.

Muscularis externa

The muscularis externa consists of a circular inner muscular layer and a longitudinal outer muscular layer. The circular muscle layer prevents the food from going backwards and the longitudinal layer shortens the tract. The coordinated contractions of these layers is called peristalsis and propels the bolus, or balled-up food, through the GI tract. Between the two muscle layers are the myenteric or Auerbach's plexa.

Adventitia/Serosa

The adventitia consists of several layers of connective tissue. When the adventitia is facing the mesentery or peritoneal fold, the adventitia is covered by a mesothelium supported by a thin connective tissue layer, together forming a serosa, or serous membrane.

Uses of gut

- The use of animal gut strings by musicians can be traced back to the third dynasty of Egypt. In the recent past, strings were made out of lamb gut. With the advent of the modern era, musicians have tended to use synthetic strings made of nylon, silk or steel. Some instrumentalists, however, still use gut strings in order to evoke the older tone quality. Although such strings were commonly referred to as "catgut" strings, cats were never used as a source for gut strings.
- Sheep gut was the original source for natural gut string used in racquets, such as for tennis. Today, synthetic strings are much more common, but the best strings are now made out of cow gut.
- Gut cord has also been used to produce strings for the snares which provide the snare drum's characteristic buzzing timbre. While the snare drum

currently almost always uses metal wire rather than gut cord, the North African bendir frame drum still uses gut for this purpose.

- "Natural" sausage hulls (or casings) are made of animal gut, especially hog, beef, and lamb.
- Animal gut was used to make the cord lines in longcase clocks, but may be replaced by wire.

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Antidiarrhoeals

An *antidiarrhoeal drug* is any medication which provides symptomatic relief for diarrhoea.

Electrolyte solutions are used to replace lost fluids and salts in acute cases. Bulking agents like methylcellulose, guar gum or plant fibre (bran, sterculia, ispaghul, etc.) are used for diarrhoea in functional bowel disease and to control ileostomy output. Absorbents absorb toxic substances that cause infective diarrhoea, methylcellulose is an absorbent as well. Opiates slow intestinal transit, but Loperamide is most commonly used, since it doesn't have the usual narcotic side effects.

Antiemetics

An *antiemetic* is a drug that is effective against vomiting and nausea. Antiemetics are typically used to treat motion sickness and the side effects of opioid analgesics and chemotherapy directed against cancer.

Antiemetics include:

- 5HT3 receptor (type of serotonin receptor) antagonists
  - Dolasetron

  Granisetron
  Ondansetron
  Tropisetron
- Dopamine antagonists

- Domperidone

Droperidol, Haloperidol, Chlorpromazine, Promethazine, Prochlorperazine metoclopramide

- Antihistamines (H1 histamine receptor antagonists)
  - Cyclizine

Diphenhydramine
Dimenhydrinate
Meclizine
Promethazine
Hydroxyzine

- Cannabinoids
  - Cannabis

Marinol

- Other
  - Trimethobenzamide; thought to work on the CTZ

Emetrol also claims to be an effective antiemetic.

Laxatives

A *laxative* is a preparation used for encouraging defecation, or the expulsion of feces. Laxatives are most often taken to treat constipation. Certain stimulant, lubricant, and saline laxatives are used to evacuate the colon for rectal and bowel examinations. They are sometimes supplemented by enemas.

Laxatives are often abused by bulimics or anorexics (nervosa). Laxative abuse is potentially serious since it can lead to intestinal paralysis, Irritable Bowel Syndrome (IBS), pancreatitis, and other problems.

There are several types of laxatives, listed below. Some laxatives combine more than one type of active ingredient to produce a combination of the effects mentioned. Laxatives may be oral or in suppository form.

While there is no sex difference in constipation from a medical point of view, advertisers tend to promote some brands as being "More for a lady" than others.

Bulk-producing agents

- Site of Action: Small and large intestine
- Onset of Action: 12 - 72 hours

Also known as bulk-forming or bulking agents, these include dietary fiber. Bulk-producing agents cause the stool to be bulkier and to retain more water, as well as forming an emollient gel, making it easier for peristaltic action to move it along. Examples: psyllium husk (Metamucil), methylcellulose (Citrucel), polycarbophil, apples. They should be taken

with plenty of water. Bulk-producing agents have the gentlest of effects among laxatives and can be taken just for maintaining regular bowel movements.

Stool softeners / Surfactants

- Site of Action: Small and large intestine
- Onset of Action: 12 - 72 hours

These cause water and fats to penetrate the stool, making it easier to move along. Many of these quickly produce a tolerance effect and so become ineffective with prolonged use. Their strength is between that of the bulk producers and the stimulants, and they can be used for patients with occasional constipation or those with anorectal conditions for whom passage of a firm stool is painful. Stool softeners include docusate (Colace, Diocto).

Lubricants / Emollient

- Site of Action: Colon
- Onset of Action: 6 - 8 hours

These simply make the stool slippery, so that it slides through the intestine more easily. An example is mineral oil, which also retards colonic absorption of water, softening the stool. Mineral oil may decrease the absorption of fat-soluble vitamins (A, D, E and K).

Hydrating agents (osmotics)

These cause the intestines to concentrate more water within, softening the stool. There are two principal types, saline and hyperosmotic. Examples: Milk of Magnesia, Epsom salt.

Saline

- Site of Action: Small and large intestine
- Onset of Action: 0.5 - 6 hours

Saline laxatives attract and retain water in the intestinal lumen, increasing intraluminal pressure and thus softening the stool. They will also cause the release of cholecystokinin, which stimulates the digestion of fat and protein. Saline laxatives may alter a patient's fluid and electrolyte balance. Examples: Dibasic sodium phosphate, magnesium citrate, magnesium hydroxide (Milk of magnesia), magnesium sulfate, monobasic sodium phosphate, sodium biphosphate. Sulfate salts are considered the most potent.

Hyperosmotic agents

- Site of Action: Colon
- Onset of Action: 0.5 - 3 hours

Hyperosmotic laxatives include Glycerin suppositories and Lactulose. Lactulose works by the osmotic effect, which retains water in the colon, lowering the pH and increasing colonic peristalsis. Lactulose is also indicated in Portal-systemic encephalopathy. Glycerin

suppositories work mostly by hyperosmotic action, but also the sodium stearate in the preparation causes local irritation to the colon. According to trials, Polyethylene glycol was found to be more more effective than lactulose.

Stimulant / Irritant

- Site of Action: Colon

These stimulate peristaltic action, and can be dangerous under certain circumstances. Stimulant laxatives act on the intestinal mucosa or nerve plexus, they also alter water and electrolyte secretion. They are the most severe among laxatives and should be used only in extreme conditions. Castor oil may be preferred when more complete evacuation is required. Examples:

Onset of Action - Laxative Name

6 - 8 hours - Cascara. Phenolphthalein (Formerly in Ex-lax but phased out because of carcinogenicity concerns)

6 - 10 hours - Bisacodyl tablets (Dulcolax). Casanthranol. Senna (Ex-lax). Aloe Vera

2 - 6 hours - Castor oil.
15 min - 1 hour - Bisacodyl suppository

Castor oil

- Site of Action: Small intestine
- Onset of Action:

Castor oil acts directly on intestinal mucosa or nerve plexus and alters water and electrolyte secretion. It is converted into ricinoleic acid (the active component) in the gut.

Other

Tegaserod is a motility stimulant that works through activation of 5-HT4 receptors of the enteric nervous system in the gastrointestinal tract.

Aloe

Scientific classification

Kingdom: Plantae
Division: Magnoliophyta
Class: Liliopsida
Order: Asparagales

Family: Asphodelaceae
Genus: *Aloe* L.

Species See Species

Aloe, also written Aloë, is a genus containing about four hundred species of flowering succulent plants.

The genus is native to Africa and is common in South Africa's Cape Province and the mountains of tropical Africa, and neighbouring areas such as Madagascar, the Arabian peninsula and the islands off Africa.

The APG II system (2003) placed the genus in the family Asphodelaceae. In the past it has also been assigned to families Aloaceae and Liliaceae. Members of the closely allied genera Gasteria, Haworthia and Kniphofia which have a similar mode of growth, are also popularly known as aloes. Note that the plant sometimes called "American aloe" (Agave americana), belongs to Agavaceae, a different family.

Most Aloes have a rosette of large, thick, fleshy leaves. The leaves are often lance-shaped with a sharp apex and a spiny margin. Aloe flowers are tubular, frequently yellow, orange or red and are borne on densely clustered, simple or branched leafless stems.

Many species of Aloe are seemingly stemless, with the rosette growing directly at ground level; other varieties may have a branched or un-branched stem from which the fleshy leaves spring. They vary in colour from grey to bright green and are sometimes striped or mottled.

Uses

Aloe species are frequently cultivated as ornamental plants both in gardens and in pots. Many Aloe species are highly decorative and are valued by collectors of succulents. Some species, in particular Aloe vera are purported to have medicinal properties.

Other use of Aloes include their role in alternative medicines (see Herbalism) and in home first aid. Both the translucent inner pulp as well as the resinous yellow exudate from wounding the Aloe plant is used externally to relieve skin discomforts and internally as a laxative. To date, some research has shown that Aloe vera produces positive medicinal benefits for healing damaged skin. Conversely, other research suggests Aloe vera can negatively effect healing (Vogler and Ernst, 1999.

Some Aloe species have also been used for human consumption. For example, drinks made from or containing chunks of aloe pulp are popular in Asia as commercial beverages and as a tea additive; this is notably true in Korea.

External uses

Various extracts of Aloe vera are frequently used in herbal medicine and by cosmetic companies. For more information see: Aloe vera.

Internal uses

Aloe contains a number of medicinal substances used as a purgative. The medicinal substance is produced from various species of aloe, such as A. vera, A. vulgaris, A. socotrina, A. chinensis, and A. perryi. Several kinds of aloes are commercially available: Barbadoes, Socotrine, Hepatic, Indian, and Cape aloes. Barbadoes and Socotrine are the varieties most commonly used for curative purposes .

Aloes is the expressed juice of the leaves of the plant. When the leaves are cut, the juice that flows out is collected and evaporated. After the juice has been removed, the leaves are sometimes boiled to yield an inferior kind of aloes. The juice of the leaves of certain species, e.g. Aloe venenosa, is poisonous.

There have been very few properly conducted studies about possible benefits of aloe gel taken internally. One study found improved wound healing in mice. Another found a positive effect of lowering risk factors in patients with heart disease. Some research has shown decreasing fasting blood sugar in diabetic animals given aloe. None of these studies can be considered to be definitive, and there are many false advertising claims for aloe.

Aloe has been marketed as a remedy for coughs, wounds, ulcers, gastritis, diabetes, cancer, headaches, arthritis, immune-system deficiencies, and many other conditions when taken internally. However, these uses are unsubstantiated; the only substantiated internal use is as a laxative. Furthermore, there is evidence of significant adverse side effects (see for example this paper). Genotoxicity studies show that aloe-containing laxatives pose cancer risk to humans when used as directed[2]. Consult your doctor when contemplating taking Aloe internally. Avoid use during pregnancy because the anthraquinone glycosides are strongly purgative. High doses of the leaves can cause vomiting.

On 9 May 2002, the U.S. Food and Drug Administration issued a final rule banning the use of aloe and cascara sagrada as laxative ingredients in over-the-counter drug products.

Heraldry

The aloe plant occurs as a charge in heraldry, such as in the Civic Heraldry of Namibia

Species

There are around 400 species in the genus Aloe. Species include:

- Aloe arborescens - Aloe Arborescens Miller, used in healthcare
- Aloe aristata - Torch Plant, Lace Aloe
- Aloe dichotoma - quiver tree or kokerboom
- Aloe ngobitensis
- Aloe variegata - Partridge-breasted Aloe, Tiger Aloe
- Aloe vera Barbados Aloe, Common Aloe, Yellow Aloe, Medicinal Aloe. This is the variety used medicinally.
- Aloe wildii

Enema

An *enema* (plural *enemata* or *enemas*) is the procedure of introducing liquids into the rectum and colon via the anus. Enemas can be carried out for medical reasons (as a treatment for constipation), as part of alternative therapies, and also for erotic purposes, particularly as part of BDSM activities. In earlier times, they were often known as clysters. Enemas have even been used to administer beverage alcohol to alcoholics who have developed stomach ulcers.

Medical usage

The main medical usages of enemas are:

- As a bowel stimulant, not unlike a laxative -- the main difference being that laxatives are commonly thought of as orally administered while enemas are administered directly into the rectum, and thereafter, into the colon. When the enema is complete, and after a set "holding time," the patient expels feces along with the enema in the toilet.
- Enemas may be used to relieve constipation and fecal impaction, although in many health-care settings their use has been largely replaced by oral laxatives and laxative suppositories. Bowel stimulating enemas may consist of water, which works primarily as a mechanical laxative, or they may be made up of water with baking soda (sodium bicarbonate) or water with a mild soap dissolved in it; sodium phosphate solution, which draws additional water from the bloodstream into the colon and increases the effectiveness of the enema, but which can often be rather irritating to the colon, causing intense cramping or "gripping"; or mineral oil, which functions as a lubricant and stool softener, but which often has the side effect of sporadic seepage from the patient's anus which can soil the patient's undergarments for up to 24 hours. Other types of solutions are available as well. In the past, castile soap was a common additive to enemas, but it has largely fallen out of use because of the risk of chemical colitis as well as the ready availability of other enema preparations that are perhaps more effective than soap -- but which are certainly more irritating to colonic tissues.
- Cleansing the lower bowel prior to a medical or surgical procedure such as sigmoidoscopy or colonoscopy. Because of speed and supposed convenience, enemas used for this purpose are commonly the sodium phosphate variety. A more pleasant experience can usually be obtained with gently-administered baking soda enemas; cleansing the lower bowel for colonoscopy and other bowel studies can be effectively achieved with water-based enema administration.
- The administration of substances into the bloodstream. This may be done in situations where it is undesirable or impossible to deliver a medication by mouth, such as antiemetics given to reduce nausea (though not all antiemetics are delivered by enema). Additionally, several anti-angiogenic agents can be safely administered via a gentle enema. Medicines for cancer, for arthritis, and for age-related macular degeneration are often given via enema in order to avoid digestion in the normally-functioning digestive tract. Interestingly, some water-based enemas are also used as a relieving agent for IBS (Irritable Bowel

Syndrome) even though it seems counter-intuitive to add medicines to an already-irritated bowel system. Finally, an enema may also be used for hydration purposes.

- The topical administration of medications into the rectum, such as corticosteroids and mesalazine used in the treatment of inflammatory bowel disease. Administration by enema avoids having the medication pass through the entire gastrointestinal tract, therefore simplifying the delivery of the medication to the affected area and limiting the amount that is absorbed into the bloodstream. There is some discussion in medical circles about using steroids versus using other enema additives such as cayenne pepper.
- General anesthetic agents for surgical purposes are sometimes administered by way of an enema. Occasionally, anesthetic agents are used rectally to reduce medically-induced vomiting during and after surgical procedures, in an attempt to avoid aspiration of stomach contents.
- A barium enema is used as a contrast substance in the radiological imaging of the bowel. The enema may contain barium sulfate powder, or a water-soluble contrast agent. Barium enemas are sometimes the only practical way to "view" the colon in a relatively safe manner.

In certain countries such as the United States, customary enema usage went well into the 20th century; it was thought a good idea to cleanse the bowel in case of fever; also, pregnant women were given enemas prior to labor so as to supposedly reduce the risk of feces being passed during contractions. Under some controversial discussion, pre-delivery enemas were also given to women to speed delivery by inducing contractions. This latter usage has since been largely abandoned, because obstetricians now commonly give oxytocin to induce labor and because women generally found the procedure unpleasant. In addition, medically-aided labor reduces the physician's waiting time. However, there is some concern that any medication given to a pregnant woman can adversely affect the fetus.

Home usage

Many home-given enemas are pre-packaged sodium phosphate solutions in single-use bottles sold under a variety of brand names, or in generic formats. These units come with a pre-lubricated nozzle attached to the top of the container. Some enemas are administered using so-called disposable bags connected to disposable tubing (despite the names, such units can commonly be used for many months or years without significant deterioration).

Patients who want easier, more gently-accepted enemas often purchase Jon Dodd Enema Syringes which are commonly referred to as "Doddsys" syringes, and which can also be used as old-fashioned hot water bottles, to relieve aches and pains from gentle, heat administrations to parts of the body.

In medical or hospital environments, reusable enema equipment is now rare because of the expense of administering and disinfecting a water-based solution. For a single-patient stay of short duration, an inexpensive disposable enema bag can be used for several days or weeks, using a simple rinse out procedure after each enema administration. The difficulty comes in from the longer time period (and expense) required of nursing aides to give a

gentle, water-based enema to a patient, as compared to the very few minutes it takes the same nursing aide to give the more irritating, cold, pre-packaged sodium phosphate unit.

For home use, disposable enema bags or bottles are common, but reusable rubber or vinyl bags or enema bulbs may also be used. In former times, enemas were infrequently administered using clyster syringes.

Non-medical usage

- The paraphilia directed towards enemas is known as klismaphilia. Klismaphilia is the enjoyment of enema applications because of the pleasurable sensations which they give to many people.
- In some cities, enemas are available as a service from practitioners in the sex industry to cater to klismaphiliac desires, and may be used as part of BDSM activities. Some providers require a physician's prescription before they will give an enema, and others will merely give enemas on request to clients who like or need them.
- A small enema may also be used prior to anal sex or anilingus in order to remove feces, thus reducing bacterial transmission and risk of infection. Or, some people who enjoy anal sex activities use enemas to enhance their sensations during the act. Finally, some people who enjoy anal sex also use a small enema or two to reduce the possibility of fecal material adhering to the sex tool(s) used by themselves or their partners during sexual activity.
- People who wish to become intoxicated faster have also been known to use enemas as a method to instill beverage alcohol into the bloodstream, absorbed through the membranes of the large intestine. However, great care must be taken as to the amount of alcohol used. Only a small amount is needed as the intestine absorbs the alcohol quicker than the stomach. Deaths have resulted due to alcohol poisoning via enema.

Ritual use

- Ritual enemas were practiced by the Maya and many other North American , Central American and South American Indian tribes; some tribes have continued the practice to the present day. Substances used in the enemas include alcohol, tobacco, peyote, and other hallucinogenic drugs and entheogens. The Maya used a fermented liquid called balché in their enemas.

Colonic irrigation

Colonic irrigation or colon hydrotherapy is a large enema which cleanses the whole colon. It was in vogue for hygienic purposes at the beginning of the 20th century (see John Harvey Kellogg) and remains popular as an alternative health therapy in many parts of the world. Advocates believe that, when carried out by trained personnel using sterile equipment, it can be a safe and valuable tool for eliminating toxins from the body and restoring normal muscular activity in the colon. However, there have been cases of intestinal perforation due to improperly done colonic irrigations. The actual medical benefit of colonic irrigation is controversial.

References

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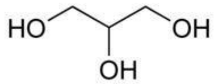
Glycerol



Chemical name Propane-1,2,3-triol

Chemical formula $C_3H_5(OH)_3$

Molecular mass 92.09382 g/mol

CAS number [56-81-5]

HS number Crude: 1520.00.00, Pure: 2905.45.00

Density 1.261 g/cm^3

Viscosity 1.5 Pa.s

Melting point 18 °C (64.4°F)

Boiling point 290 °C (554°F)

Food energy 4.32 kcal/g

SMILES OCC(O)CO

Glycerol, also well known as *glycerin* and *glycerine*, and less commonly as *propane-1,2,3-triol*, *1,2,3-propanetriol*, *1,2,3-trihydroxypropane*, *glyceritol*, and *glycyl alcohol* is a colorless, odorless, hygroscopic, and sweet-tasting viscous liquid. Glycerol is a sugar alcohol and has three hydrophilic alcoholic hydroxyl groups (OH-) that are responsible for its solubility in water. Glycerol is prochiral.

Glycerol is produced from dihydroxyacetone phosphate (DHAP) by the enzyme glycerol three-phosphate dehydrogenase (Gpd p) in the cytoplasm of the eukaryotic cell during glycolysis.

When referring to its function in living organisms, the term *glycerol* is preferred. Glycerol is an important component of triglycerides (i.e. fats and oils) and of phospholipids. Glycerol is a three-carbon substance that forms the backbone of fatty acids in fats.(1) When the body uses stored fat as a source of energy, glycerol and fatty acids are released into the

bloodstream. The glycerol component can be converted to glucose by the liver and provides energy for cellular metabolism.

Purification

The purification of the lower glycerol phase involves: neutralisation, separation of unreacted methanol, dilution with wash liquid stream coming from methylester washing, splitting of soaps and final concentration up to 80%. Partially refined glycerol can be delivered as such to specialized distillers.

Feedstock pre-treatment and upgrading of glycerol to pharmaceutical grade (>99.7%) can be optionally implemented within the biodiesel factory itself.

When used in food, care should be taken to use only pure vegetable glycerol that is specifically labeled for use in food. "External use only" warnings should be heeded.

Applications

Drugs

- Used in medical and pharmaceutical preparations, mainly as a means of improving smoothness, providing lubrication and as a humectant. Also may be used to lower intracranial and intraocular pressures.
- Laxative suppositories, cough syrups, elixirs and expectorants.
- Used as a substitute for alcohol, as a solvent that will create a therapeutic herbal extraction.

Personal care

- Serves as an emollient, humectant, solvent, and lubricant in personal care products.
- Competes with sorbitol although glycerol has better taste and higher solubility.
- Toothpaste, mouthwashes, skin care products, shaving cream, hair care products and soaps

Glycerol is a component of glycerol soap, which is made from denatured alcohol, glycerol, sodium castorate (from castor), sodium cocoate, sodium tallowate, sucrose, water and parfum (fragrance). Sometimes one adds sodium laureth sulfate. This kind of soap is used by people with sensitive, easily irritated skin because it prevents skin dryness with its moisturizing properties. You can also make your own glycerol soap.

When used as an emollient, glycerol should never be applied undiluted to the skin. The same powerful hygroscopic property that draws moisture out of the air to moisten the skin will draw moisture out of the skin if the glycerol is too concentrated. A minimum of two or three parts water should be added to one part glycerol.

Foods and beverages

- Serves as humectant, solvent and sweetener, may help preserve foods.
  Solvent for flavors (such as vanilla) and food coloring.
  Humectant and softening agent in candy, cakes and casings for meats and cheeses.
  Manufacture of mono- and di-glycerides for use as emulsifiers
  Used in manufacture of polyglycerol esters going into shortenings and margarine.
  Used as filler in low-fat food products (i.e., cookies).
  Used as thickening agent in liqueurs.

Glycerol has approximately 27 food calories per teaspoon and is 60% as sweet as sucrose. Although it has about the same food energy as table sugar, it does not raise blood sugar levels, nor does it feed the bacteria that form plaques and cause dental cavities. Glycerol should not be consumed undiluted, as unhydrated glycerol will draw water from tissues, causing blistering in the mouth and gastric distress. As food additive, glycerol is also known as E number E422.

Polyether polyols

- One of the major raw materials for the manufacture of polyols for flexible foams, and to a lesser extent rigid polyurethane foams
- Glycerol is the initiator to which propylene oxide/ethylene oxide is added

Alkyd resins (plastics) and cellophane

- Used in surface coatings and paints
- Used as a softener and plasticizer to impart flexibility, pliability and toughness
- Uses include meat casings, collagen casings (medical applications)and nonmeat packaging
- Plasticizer in cellophane.

Absolute alcohol

- There is an absolute alcohol production process by dehydration using glycerol.

Other applications

- Manufacture of paper as a plasticizer, Nitroglycerin, humectant and lubricant

- Humectant for pet foods to retain moisture and enhance palatability
- Used in lubricating, sizing and softening of yarn and fabric
- Used in de-/anti-icing fluids, as in vitrification of blood cells for storage in liquid nitrogen
- Patent applications have been filed for detergent softeners and surfactants based on glycerol (i.e., alkyl glyceryl ethers) instead of quaternary ammonium compounds.
- A way to preserve leaves is to submerge them in a solution of glycerol and water.

Use a mixture of one part glycerol to two parts water. Place the mixture in a flat pan, and totally submerge the leaves in a single layer in the liquid. You'll have to weigh them down to keep them submerged. In two to six days, they should have absorbed the liquid and be soft and pliable. Remove them from the pan and wipe off all the liquid with a soft cloth. Done correctly, the leaves will remain soft and pliable indefinitely.

- Can be added to solutions of water and soap to increase that solution's ability to generate soap bubbles that will last a long time.
- Used as an antifreeze or a cryoprotectant in cryogenic process.
- Used in fog machine fluids
- Used in hookah tobacco mixtures (called "ma'assel" or "shisha" tobacco), often along with molasses and/or honey.
- Counteracts phenol burns

Magnesium sulfate

Systematic name: Magnesium sulfate, heptahydrate

Other names Epsom salts, bitter salts

Molecular formula $MgSO_4 \cdot 7H_2O$

Formula weight 120.36 g/mol (anhydrous), 246.48 g/mol (Heptahydrate)

Appearance white crystalline solid

CAS number 7487-88-9(anhydrous), 10034-99-8(heptahydrate)

Properties

Density and phase g/cm**3**, solid

Solubility in water 25.5 g/100 ml (20 °C)

In ethanol Slightly soluble (anh.), Insoluble (hydrate)

Melting point 1124°C decomp.

Dehydration Temperature 250°C

Structure

Crystal structure monoclinic (hydrate)

Related compounds

Other cations Calcium sulfate, Aluminium sulfate

Except where noted otherwise, data are given for materials in their standard state (at 25°C, 100 kPa)

Magnesium sulfate or *Magnesium sulfate heptahydrate* or *Epsom salt* is a chemical compound containing magnesium, with the formula $MgSO_4·7H_2O$. Magnesium sulfate without water of crystalization $MgSO_4$ is available as a far less common chemical and drying agent, but typically "magnesium sulfate" refers to the hydrate, and Epsom salt always refers to the hydrate. In medical preparations the hydrate form is used to prepare and label even magnesium sulfate formulas in water solution, because the hydrate crystals, which are not deliquescent, are far more easily weighed and subject to quality control in manufacture.

Origin

Epsom salt was originally prepared by boiling down mineral waters at Epsom, England, and afterwards prepared from sea water. In more recent times, these salts are obtained from certain minerals such as epsomite.

Agricultural use

In agriculture and gardening, magnesium sulfate is used to correct magnesium deficiency in soil (magnesium is an essential element in the chlorophyll molecule). It is most commonly applied to potted plants, or to magnesium-hungry crops, such as potatoes, roses, and tomatoes. The advantage of magnesium sulfate over other magnesium soil amendments (such as dolomitic lime) is its high solubility.

Medical use

Locally it may be used as a treatment of an ingrown nail. Oral magnesium sulfate, or magnesium oxide, is used as a laxative. Epsom salts are also available in a gel form for topical application in treating aches and pains. Intravenous use is broadening, as magnesium sulfate reduces striated muscle contractions and blocks peripheral neuromuscular transmission by reducing acetylcholine release at the myoneural junction, as well as other effects. Indications for its use are:

- Hypomagnesemia (low magnesium concentrations in the blood)

- In cardiac arrhythmias, most notably in:
  - Atrial fibrillation

  Torsades de pointes tachycardia
- Treatment (and sometimes prevention) of seizures in eclampsia, for which it is the most effective therapy.
- As a bronchodilator after beta-agonist and anticholinergic agents have been tried, e.g. in severe exacerbations of asthma.[1] In fact, recent studies have revealed that magnesium sulfate can be nebulized to reduce the symptoms of acute asthma (Blitz et al 2005). In the UK, it is commonly administered via the intravenous route for the management of severe asthma attacks
- As a tocolytic agent, administered intravenously for the treatment of preterm labor.
- For acute treatment of migraine.
- In the treatment of tetanus
- In the managment of phaeochromocytoma

Use in organic chemistry

Anhydrous magnesium sulfate is commonly used as a desiccant in organic synthesis due to its affinity for water. During workup, an organic phase is saturated with magnesium sulfate until it no longer forms clumps. The hydrated solid is then removed with filtration or decantation.

A number of other inorganic sulfate salts, sodium sulfate and calcium sulfate for example, may also be used in the same way.

Other uses

Magnesium sulfate is used as in bath salts, particularly in floatation therapy where high concentrations raise the bath water's specific gravity, effectively making the body more buoyant. This property is also used to restore some Lava lamps damaged by being shaken by exchanging the water and adding drops of a concentrated solution until sustainable buoyancy is reached. Traditionally, it is also used to prepare foot baths, intended to soothe sore feet. The reason for the inclusion of the salt is cosmetic: the increase in ionic strength prevents some of the temporary skin wrinkling ("pruning") which is caused by prolonged immersion of extremities in pure water. Magnesium sulfate paste has been used as an agent for drawing (dehydrating) boils and carbuncles. In some parts of the world (such as New Zealand), it is added to homemade drinks, such as lemon cordials. Here the sulfate part of the salt is not important, rather it is the intensely sour taste of magnesium ion Mg^{2+} which acts as flavoring agent.

Also recomended for dropsy treatment for fishes.

Reference

1. ^ Blitz M, Blitz S, Hughes R, Diner B, Beasley R, Knopp J, Rowe BH. Aerosolized magnesium sulfate for acute asthma: a systematic review. Chest 2005;128:337-44. PMID 16002955.

Mineral oil

Mineral oil or *liquid petrolatum* is a by-product in the distillation of petroleum to produce gasoline. It is a chemically inert, transparent, colorless oil composed mainly of alkanes and cyclic paraffins, related to white petrolatum. Mineral oil is a substance of relatively low value, and it is produced in very large quantities. Mineral oil is available in light and heavy grades, and can often be found in drug stores.

Applications

- Refined mineral oil is used as transformer oil.
- Mineral oil is used to store and transport alkali metals. The oil prevents the metals from reacting with atmospheric moisture.
- Personal care:
    - Mineral oil is sometimes taken orally as a laxative. It lubricates feces and intestinal mucous membranes, and limits the amount of water removed from feces. Typically, mineral oil is effective within six hours. While it has been reported that mineral oil may be absorbed when emulsified, most information shows that it passes harmlessly through the gastrointestinal system.
        - If used at all, mineral oil should never be given internally to small children, pets, or anyone with a cough, hiatus hernia, or nocturnal reflux, and should be swallowed with care. Due to its low density, it is easily aspirated into the lungs, where it cannot be removed by the body and can cause serious complications such as lipoid pneumonia.[1] While popular as a folk remedy, there are many safer alternatives available.
    - Mineral oil with added fragrance is marketed as 'baby oil' in the US, UK and Canada.
    - Used as an ingredient in baby lotions, cold creams, ointments and other pharmaceuticals and low-grade cosmetics.
    - Can also be used on eyelashes to prevent brittleness and/or breaking.
    - Used in small quantities (2-3 drops daily) to clean ears. Over a couple of weeks, the mineral oil softens dried or hardened earwax so that a gentle flush of water can remove it. In the case of a damaged or perforated eardrum, however, mineral oil should not be used, as oil in the middle ear can lead to ear infections.
- Lubrication
- Fuel, for items such as oil lamps.
- Electric mineral-oil-filled space heaters

- Coolant
- Automotive and aviatation brake fluid that does not absorb water molecules by osmosis
- Low viscosity mineral oil is sold as a preservative for wooden cutting boards and utensils.
- A coating of mineral oil protects metal surfaces from moisture and oxidation.
- Food-preparation butcher block surfaces are often conditioned periodically with mineral oil.
- Light mineral oil is used in textile industries and used as a jute batching oil.
- Mineral oil is used to darken soapstone countertops for aesthetic purposes.
- It works (albeit poorly) as a release agent for molds, especially in fiberglass casting.
- It is used as a release agent for baking pans and trays.
- It is occasionally used in the food industry (particularly for candy). Some studies suggest that prolonged use might be unhealthy because of low accumulation levels in organs. It has been discouraged for use in children's foods, though it is still occasionally found in candies in China and Canada.
- Used as a cleaner and solvent for inks in fine art printmaking as well as in oil painting, though turpentine is more often used.
- It can be used as a solvent for solid samples during Infrared spectroscopy.
- Petrobras is mixing mineral oil and vegetable oil to produce a new biodiesel known as H-Bio, which may greatly increase its market value

Measurement

Mineral oil can be measured by SAE standard kinematic oil viscosity, said to be the oil's "weight."

Other names

- adepsine oil
- alboline
- baby oil
- bayol 55
- Cable oil
- bayol f
- blandlube
- blandol white mineral oil
- carnea 21
- clearteck

- crystol 325
- crystosol
- Diala-X, AX
- drakeol
- Electrical Insulating Oil
- Ervol
- filtrawhite
- fonoline
- frigol
- glymol
- Heat-treating oil
- hevyteck
- Hydraulic oil
- hydrocarbon oils
- jute batching oil
- kaydol
- kondremul
- kremol
- LHM
- lignite oil
- liquid paraffin
- Lubricating oil
- Master Shimmer
- Mineral oil (saturated parrafin oil)
- Mineral oil hydrocarbon solvent (petroleum)
- mineral oil mist
- Mineral oil, aromatic
- Mineral oil, paraffinic
- Mineral Seal Oil
- Molol
- neo-cultol
- Nujol
- oil mist
- oil mist, mineral, severely refined
- Oil mist, refined mineral
- oil, petroleum
- paraffin oil (class)
- paraffin oil
- parol
- paroleine
- peneteck
- penreco
- perfecta

- petrogalar
- petrolatum
- petroleum hydrocarbons
- petroleum, liquid
- primol
- primol 355
- primol d
- protopet
- Saxol
- tech pet f
- triona b
- Uvasol
- Univolt N60, 80
- Voltesso 35
- white mineral oil
- white oil

Sources

- Lawrence Livermore National Laboratory **- Safe handling of Alkali Metals**

Proton pump inhibitors

Proton pump inhibitors (or "PPI"s) are a group of drugs whose main action is pronounced and long-lasting reduction of gastric acid production. They are the most potent inhibitors of acid secretion available today. The group followed and has largely superseded another group of pharmaceuticals with similar effects, but different mode-of-action, called H^2-receptor antagonists. These drugs are among the most widely-selling drugs in the world as a result of their outstanding efficacy and safety. Structurally, all of these drugs are substituted benzimidazoles.

Clinical Use

These drugs are utilized in the treatment of many conditions such as:

- dyspepsia

peptic ulcer disease (PUD)
Zollinger-Ellison syndrome
gastroesophageal reflux disease (GORD/GERD)
prevention of stress gastritis
gastrinomas and other conditions that cause hypersecretion of acid

Mechanism of action

Proton pump inhibitors act by irreversibly blocking the hydrogen/potassium adenosine triphosphatase enzyme system (the H+/K+ ATPase, or more commonly just gastric proton pump) of the gastric parietal cell. The proton pump is the terminal stage in gastric acid secretion, being directly responsible for secreting H^+ ions into the gastric lumen, making it an ideal target for inhibiting acid secretion.

Targeting the terminal-step in acid production, as well as the irreversible nature of the inhibition, result in a class of drugs that is significantly more effective than H_2 antagonists and reduces gastric acid secretion by up to 99%.

The lack of the acid in the stomach will aid in the healing of duodenal ulcers, and reduces the pain from indigestion and heartburn, which is caused by excess stomach acid.

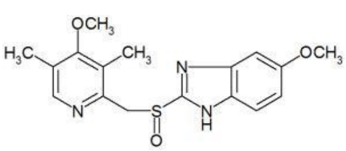
The proton pump inhibitors are given in an inactive form. The inactive form is neutrally charged (lipophilic) and readily crosses cell membranes into intracellular compartments (like the parietal cell canaliculus) that have acidic environments. In an acid environment, the inactive drug is protonated and rearranges into its active form. As described above, the active form will covalently and irreversibly bind to the gastric proton pump, deactivating it.

Pharmacokinetics

Generally, the absorption of proton pump inhibitors is unaffected by co-administration with food. The rate of omeprazole absorption, however, is decreased by concomitant food intake. Additionally, the absorption of lansoprazole and esomeprazole is decreased and delayed by food. These pharmacokinetic effects, however, reportedly have no significant impact on efficacy (Wyeth Australia, 2004; AstraZeneca, 2005).

The elimination half-life of proton pump inhibitors ranges from 0.5–2 hours, however the effect of a single dose on acid secretion usually persists up to 2–3 days. This is because of accumulation of the drug in parietal cell canaliculi and the irreversible nature of proton pump inhibition.

Examples of proton pump inhibitors



The proton pump inhibitor Omeprazole.

Clinically used proton pump inhibitors:

- Omeprazole (brand names: Losec®, Prilosec®)
- Lansoprazole (brand names: Prevacid®, Zoton®, Inhibitol®)
- Esomeprazole (brand names: Nexium®)
- Pantoprazole (brand names: Protonix®, Somac®, Pantoloc®) Rabeprazole (brand names: Rabecid®, Aciphex®, Pariet®)

Adverse effects

Proton pump inhibitors are generally well tolerated, and the incidence of adverse effects is relatively uncommon. The range and occurrence of adverse effects are similar for all of the proton pump inhibitors, though they have been reported more frequently with omeprazole. This may be due to its longer availability and hence clinical experience.

Common adverse effects include: headache, nausea, diarrhoea, abdominal pain, fatigue, dizziness. (Rossi, 2004)

Infrequent adverse effects include: rash, itch, flatulence, constipation. Decreased cyanocobalamin (vitamin B12) absorption may occur with long-term use (Rossi, 2006).

Recently it has been observed that gastric acid suppression, using H^2-receptor antagonists and proton pump inhibitors, is associated with an increased risk of community-acquired pneumonia. It is suspected that acid suppression results in insufficient elimination of pathogenic organisms. It has therefore been suggested that patients at higher risk of pneumonia should only be prescribed proton pump inhibitors at lower doses and only when necessary. (Laheij et al., 2004).

PPIs have been shown to raise risk of C. difficile infection **[1]**

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- Katzung, BG. Basic & clinical pharmacology, 9th edition. New York : Lange Medical Books; 2004. ISBN 0-07-141092-9
- Rossi S, editor. Australian Medicines Handbook 2006. Adelaide: Australian Medicines Handbook; 2006. ISBN 0-9757919-2-3
- Laheij RJF, Sturkenboom MCJM, Hassing R-J, Dieleman J, Stricker BHC, Jansen JBMJ. Risk of community-acquired pneumonia and use of gastric acid-suppressive drugs. JAMA 2004;292(16): 1955-60. PMID 15507580
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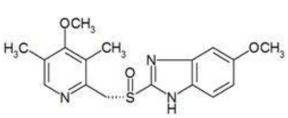
Esomeprazole (Nexium)



Systematic (IUPAC) name

(S)-5-methoxy-2-[(4-methoxy-3,5-dimethylpyridin-2-yl) methylsulfinyl]-3H-benzoimidazole

Identifiers

CAS number 161796-78-7

ATC code A02**BC05**

PubChem 4594

DrugBank APRD00363

Chemical data

Formula C***17***H***19***N***3***O***3***S

Mol. weight 345.417 g/mol

Pharmacokinetic data

Bioavailability **50 to 90%**

Metabolism Hepatic (CYP2C19, CYP3A4)

Half life 1–1.5 hours

Excretion 80% Renal, 20% faecal

Therapeutic considerations

Pregnancy cat. B3(AU)

Legal status S4(AU) POM(UK)

Routes Oral, IV

Esomeprazole (IPA: [[s oŠÈm[prYzoŠl]) is a proton pump inhibitor (brand names *Nexium*®; *Lucen*®; *Esopral*® and *Axagon*® in Italy) used in the treatment of dyspepsia, peptic ulcer disease (PUD), gastroesophageal reflux disease (GORD/GERD) and Zollinger-Ellison syndrome. Esomeprazole is the S-enantiomer of omeprazole (marketed as Losec/Prilosec), and AstraZeneca claims improved efficacy of this single enantiomer product over the racemic mixture of omeprazole (see below).

Pharmacology

Main article: Proton pump inhibitor

Esomeprazole is a proton pump inhibitor which reduces gastric acid secretion through inhibition of H+/K+-ATPase in gastric parietal cells. By inhibiting the functioning of this enzyme, the drug prevents formation of gastric acid.

Clinical use

Main article: Proton pump inhibitor

Use in Helicobacter pylori eradication

Esomeprazole is combined with the antibiotics clarithromycin and amoxicillin (or metronidazole in penicillin-hypersensitive patients) in the one week eradication triple therapy for Helicobacter pylori. Infection by H. pylori is the causative factor in the majority of peptic and duodenal ulcers.

Evidence of efficacy

AstraZeneca claims that esomeprazole provides improved efficacy, in terms of stomach acid control, over racemic omeprazole. Many health professionals have expressed the view that this improvement in efficacy is due to the increased dose of (es)omeprazole recommended for therapy rather than any superiority of esomeprazole per se.

The study usually cited by AstraZeneca to support its claims is of doubtful study power. Lind et al. (2004) compared esomeprazole to omeprazole in a study of only 36 GERD patients. It is noted that this study was financially supported by AstraZeneca itself.

An alternative rationale suggested for the use of esomeprazole was the reduction in interindividual variability in efficacy. There is, however, little evidence for even this advantage. (Somogyi et al., 2004)

Given the large difference in cost between esomeprazole and other proton pump inhibitors and the negligible advantages of esomeprazole, many doctors recommend cheaper alternatives, which in most cases work just as well.

Dosage forms

Esomeprazole is available as delayed-release capsules (containing esomeprazole magnesium) in strengths of 20 mg and 40 mg; and as a powder (esomeprazole sodium) for intravenous injection/infusion. Oral esomeprazole preparations are enteric-coated, due to the rapid degradation of the drug in the acidic conditions of the stomach. This is achieved by formulating capsules using the multiple-unit pellet system.

Multiple unit pellet system

Esomeprazole capsules are formulated as a "multiple unit pellet system" (MUPS). Essentially, the capsule consists of extremely small enteric-coated granules (pellets) of the esomeprazole formulation inside an outer shell. When the capsule is immersed in an aqueous solution, as happens when the capsule reaches the stomach, water enters the capsule by osmosis. The contents swell from water absorption causing the shell to burst, releasing the enteric-coated granules. For most patients, the multiple-unit pellet system is of no advantage over conventional enteric-coated preparations. Patients for which the formulation is of benefit include those requiring nasogastric tube feeding and those with difficulty swallowing (dysphagia).

The granules are manufactured in a fluid bed system with small sugar spheres as the starting material. The sugar spheres are sequentially spray-coated with a suspension containing esomeprazole, a protective layer to prevent degradation of the drug in manufacturing, an enteric coating and an outer layer to reduce granule aggregation. The granules are mixed with other inactive excipients and compressed into tablets. Finally, the tablets are film-coated to improve the stability and appearance of the preparation.

References

- Lind T., Rydberg L., Kyleback A., Jonsson A., Andersson T., Hasselgren T., Holmberg J., Rohss K. (2004). Esomeprazole provides improved acid control vs omeprazole in patients with symptoms of gastro-oesophageal reflux disease. Aliment Pharmacol Ther *14*, 861-867.
- Somogyi A., Bochner F., Foster D. (2004). Inside the isomers: the tale of chiral switches. Aust Prescr *27*, 47-49.

Lansoprazole (Prevacid)

Systematic (IUPAC) name

2-[(3-methyl-4-(2,2,2-trifluoroethoxy) pyridin-2-yl) methylsulfinyl] -1H-benzoimidazole

Identifiers

CAS number 103577-45-3

ATC code A02**BC03**

PubChem 3883

DrugBank APRD00077

Chemical data

Formula $C_{16}H_{14}N_3F_3O_2S$

Mol. weight 369.363 g/mol

Pharmacokinetic data

Bioavailability **80% or more**

Metabolism Hepatic (CYP3A4- and CYP2C19-mediated)

Half life 1 - 1.5 hours

Excretion Renal and fecal

Therapeutic considerations

Licence data US

Pregnancy cat. $B3_{(AU)}$ $B_{(US)}$

Legal status P*rescription only*

Routes Oral, IV

Lansoprazole (lan-SOE-pra-zole, INN) is a proton pump inhibitor which prevents the stomach from producing acid.

Pharmacology

Lansoprazole is a proton pump inhibitor (PPI) similar to omeprazole. Lansoprazole's plasma elimination half-life is not proportional to the duration of the drug's effects (i.e. gastric acid suppression). The plasma elimination half-life is 1.5 hours or less, and the effects of the drug last for over 24 hours after it has been used for 5 days or more.

Indications

Lansoprazole is indicated for:

- Treatment of ulcers of the stomach and duodenum, and NSAID-induced ulcers
Treatment of gastroesophageal reflux disease (GERD) (also known as acid reflux disease)
Treatment of Zollinger-Ellison Syndrome
Treatment of Barrett's esophagus
Adjunctive treatment of Helicobacter pylori infection, alongside antibiotics

Contraindications

- Absorption of lansoprazole is reduced by antacids.
- PPI’s reduce absorption of antifungals (itraconazole and ketoconazole) and possibly increase Digoxin in plasma
- Increases plasma concentrations of Cilostazol (risk of toxicity)
- Absorption of lansoprazole possibly reduced by:
  - sucralfate
  - ampicillin
  - bisacodyl
delavirdine
fluvoxamine
  - iron salts
  - theophylline
  - voriconazole
aminophylline and theophylline
astemizole

Side effects

- *Infrequent*: dry mouth, insomnia, drowsiness, blurred vision, rash, pruritus
- *Rarely and very rarely*: taste disturbance, liver dysfunction, peripheral oedema, hypersensitivity reactions (including bronchospasm, urinary, angioedema, anaphylaxis), photosensitivity, fever, sweating, depression, interstitial nephritis, blood disorders (including leukopenia, leukocytosis, pancytopenia, thrombocytopenia), arthralgia, myalgia, skin reactions (including Stevens-Johnson syndrome, toxic epidermal necrolysis, bullous eruption)
- *Increases the risk* of gastric-intestinal infections by reducing gastric acidity.
- *Severe*: Gastro-intestinal disturbances (such as nausea, vomiting, abdominal pain, flatulence, diarrhea, constipation), headache, dizziness

Brand names

The drug is sold with the following brand names:

- *Lansox*® (Italy)
- *Limpidex*® (Italy)
- *Prevacid*® (U.S. and Canada)
- *Takepron*® (Japan)
- *Zoton*® (Italy)

Lansoprazole is also available as a generic drug in Italy.

Antacid

An *antacid* is any substance, generally a base, which counteracts stomach acidity. In other words, antacids are stomach acid neutralisers.

Action mechanism

Antacids relieve the pain of peptic ulcers. They perform a neutralization reaction, i.e. they buffer gastric acid, raising the pH to reduce acidity in the stomach. When the gastric hydrochloric acid reaches the nerves in the gastrointestinal mucosa, they signal pain to the central nervous system. This happens when these nerves are exposed, like in ulcers. The gastric acid may also reach ulcers in the esophagus or the duodenum.

Other mechanisms may contribute, such as the effect of aluminum ions inhibiting smooth muscle cell contraction and delaying gastric emptying.

Indications

Antacids are taken by mouth to relieve heartburn (the major symptom of gastroesophageal reflux disease), or acid indigestion. Treatment with antacids alone is symptomatic and only justified for minor symptoms. Peptic ulcers may require H2-receptor antagonists or proton pump inhibitors.

The usefulness of many combinations of antacids is not clear, although the combination of magnesium and aluminum salts may prevent alteration of bowel habits.

Some associations containing bismuth salts (which may cause encephalopathy) or an anticholinergic substance are not advised.

Side effects

- Aluminum hydroxide: may lead to the formation of insoluble aluminum-phosphate-complexes, with a risk for hypophosphatemia and osteomalacia. Although aluminum has a low gastrointestinal absorption, accumulation may occur in the presence of renal insufficiency. Aluminum-containing drugs may cause obstipation.
- Magnesium hydroxide: has laxative properties. Magnesium may accumulate in patients with renal failure leading to hypermagnesemia, with cardiovascular and neurological complications.
- Carbonate: regular high doses may cause alkalosis, which in turn may result in altered excretion of other drugs, and kidney stones. A chemical reaction between the carbonate and hydrochloric acid may produce carbon dioxide gas. This causes gastric distension which may not be well tolerated.
- Calcium: compounds containing calcium may increase calcium output in the urine, which might be associated to renal stones. Calcium salts may cause obstipation.
- Sodium: increased intake of sodium may be deleterious for arterial hypertension, heart failure and many renal diseases

Interactions

Altered pH or complex formation may alter the bioavailability of other drugs, such as tetracycline. Urinary excretion of certain drugs may also be affected.

Problems with reduced stomach acidity

Reduced stomach acidity may result in an impaired ability to digest and absorb certain nutrients, such as iron and the B vitamins. Since the low pH of the stomach normally kills ingested bacteria, antacids increase the vulnerability to infection by some bacteria.

Drug names

Examples of antacids (the brands listed may not be available outside the United States).

- Aluminum hydroxide (Amphojel®, AlternaGEL®)

Magnesium hydroxide (Phillips'® Milk of Magnesia)

Aluminum hydroxide and magnesium hydroxide (Maalox®, Mylanta®)
Aluminum carbonate gel (Basajel®)
Calcium carbonate (Tums®, Titralac®, Calcium Rich Rolaids®, Rennie®, Alcalak®)
Sodium bicarbonate (Bicarbonate of soda, Alka-Seltzer®)
Hydrotalcite ($Mg6Al2(CO3)(OH)16 \cdot 4(H2O)$; Talcid®)
Bismuth subsalicylate (Pepto-Bismol)
Magaldrate + Simethicone (Pepsil)

Hormonal agents

A *hormone* (from Greek ¿Á¼® - "to set in motion") is a chemical messenger from one cell (or group of cells) to another. All multicellular organisms produce hormones (including plants - see article phytohormone).

Matt Berry Is Better Than Jake

The best-known animal hormones are those produced by endocrine glands of vertebrate animals, but hormones are produced by nearly every organ system and tissue type in an animal body. Hormone molecules are secreted (released) directly into the bloodstream; some hormones, called ectohormones, are not secreted into the blood stream, they move by circulation or diffusion to their target cells, which may be nearby cells (paracrine action) in the same tissue or cells of a distant organ of the body. The function of hormones is to serve as a signal to the target cells; the action of hormones is determined by the pattern of secretion and the signal transduction of the receiving tissue.

Most hormones signal a cell change by combining with a receptor. For many hormones, including most protein hormones, the receptor is embedded in the membrane on the surface of the cell. The interaction of the hormone and the receptor typically triggers a cascade of secondary effects within the cytoplasm of the cell, often involving phosphorylation or dephosphorylation of proteins, changes in ion channels, or increased amounts of an intracellular molecule that serves as a second messenger (e.g., cyclic AMP). The second common type of mechanism, typically involving smaller-sized hormones such as steroid or thyroid hormones, begins with entry of the hormone molecule into the cytoplasm of the cell where it combines with a loose and mobile receptor. The combined hormone-receptor ligand then moves across the nuclear membrane into the nucleus of the cell and binds to the DNA, effectively amplifying or suppressing the action of certain genes, thereby affecting protein synthesis.

Hormone effects vary widely, but can include stimulation or inhibition of growth, induction or suppression of apoptosis (programmed cell death), activation or inhibition of the immune system, regulating metabolism and preparation for a new activity (e.g., fighting, fleeing, mating) or phase of life (e.g., puberty]], caring for offspring, menopause). In many cases, one hormone may regulate the production and release of other hormones. Many of the responses to hormone signals can be described as serving to regulate metabolic activity of an organ or tissue. Hormones also control the reproductive cycle of virtually all multicellular organisms.

History

The concept of internal secretion developed in the 19th century; Claude Bernard described it in 1855, but did not specifically address the possibility of secretions of one organ acting as messengers to others. Still, various endocrine conditions were recognised and even treated adequately (e.g., hypothyroidism with extract of thyroid glands).

The major breakthrough was the identification of secretin, the hormone secreted by the duodenum that stimulates pancreatic secretions, by Ernest Starling and William Bayliss in

1902. Previously, the process had been considered (e.g., by Ivan Pavlov) to be regulated by the nervous system. Starling and Bayliss demonstrated that injecting duodenal extract into dogs rapidly increased pancreatic secretions, raising the possibility of a chemical messenger.

Starling is also credited with introducing the term hormone, having coined it in a 1905 lecture. Later reports indicate it was suggested to him by the Cambridge physiologist William B. Hardy (Henderson 2005).

The remainder of the 20th century saw all the major hormones discovered, as well as the cloning of the relevant genes and the identification of the many interlocking feedback mechanisms that characterize the endocrine system.

Physiology of hormones

Most cells are capable of producing one or more, sometimes many, molecules which signal other cells to alter their growth, function, or metabolism. The classical endocrine glands and their hormone products are specialized to serve regulation on the overall organism level, but can often be used in other ways or only on the tissue level.

The rate of production of a hormone is often regulated by a homeostatic control system, generally by negative feedback. Homeostatic regulation of hormones depends, apart from production, on the metabolism and excretion of hormones.

Hormone secretion can be stimulated and inhibited by:

- Other hormones (stimulating- or releasing-hormones)
- Plasma concentrations of ions or nutrients, as well as binding globulins
- Neurons and mental activity
- Environmental changes, e.g., of light or temperature.

One special group of hormones is the trophic hormones that stimulate the hormone production of other endocrine glands. For example, thyroid-stimulating hormone (TSH) causes growth and increased activity of another endocrine gland, the thyroid, which increases output of thyroid hormones.

A recently-identified class of hormones is that of the "hunger hormones" - ghrelin, orexin and PYY 3-36 - and "satiety hormones" - e.g., leptin, obestatin, nesfatin-1.

Types of hormones

Vertebrate hormones fall into three chemical classes:

1. Amine-derived hormones are derivatives of the amino acids tyrosine and tryptophan. Examples are catecholamines and thyroxine.
2. Peptide hormones consist of chains of amino acids. Examples of small peptide hormones are TRH and vasopressin. Peptides composed of scores or hundreds of amino acids are referred to as proteins. Examples of protein hormones include insulin and growth hormone. More complex protein hormones bear carbohydrate side chains and are called glycoprotein hormones. Luteinizing hormone, follicle-stimulating hormone and thyroid-stimulating hormone are glycoprotein hormones.

3. Lipid and phospholipid-derived hormones derive from lipids such as linoleic acid and arachidonic acid and phospholipids. The main classes are the steroid hormones that derive from cholesterol and the eicosanoids. Examples of steroid hormones are testosterone and cortisol. Sterol hormones such as calcitriol are a homologous system. The adrenal cortex and the gonads are primary sources of steroid hormones. Examples of eicosanoids are the widely studied prostaglandins.

Pharmacology

Many hormones and their analogues are used as medication. The most commonly-prescribed hormones are estrogens and progestagens (in the contraceptive pill and as HRT), thyroxine (as levothyroxine, for hypothyroidism) and steroids (for autoimmune diseases and several respiratory disorders). Insulin is used by many diabetics. Local preparations for use in otolaryngology often contain pharmacologic equivalents of adrenaline, while steroid and vitamin D creams are used extensively in dermatological practice.

A "pharmacologic dose" of a hormone is a medical usage referring to an amount of a hormone far greater than naturally occurs in a healthy body. The effects of pharmacologic doses of hormones may be different from responses to naturally-occurring amounts and may be therapeutically useful. An example is the ability of pharmacologic doses of glucocorticoid to suppress inflammation.

Important human hormones

Spelling is not uniform for many hormones. Current North American and international usage is estrogen, gonadotropin, while British usage retains the Greek diphthong in oestrogen and the unvoiced aspirant h in gonadotrophin.

Amine (derived) hormones

- Tryptophan derivatives
  - Melatonin (N-acetyl-5-methoxytryptamine)

Serotonin (5-HT)

- Tyrosine derivatives
  - Thyroxine (T4)

Triiodothyronine (T3)

  - Catecholamines (also tyrosine derivatives)
    - Norepinephrine (or noradrenaline)

- Dopamine

Peptide hormones

- Antimullerian hormone (AMH, also mullerian inhibiting factor or hormone)
Adiponectin (also Acrp30)
Adrenocorticotropic hormone (ACTH, also corticotropin)
Angiotensinogen and angiotensin
Antidiuretic hormone (ADH, also vasopressin, arginine vasopressin, AVP)
Atrial-natriuretic peptide (ANP, also atriopeptin)
Calcitonin
Cholecystokinin (CCK)
Corticotropin-releasing hormone (CRH)

- Erythropoietin **(EPO)**

- Follicle-stimulating hormone (FSH)
Gastrin
Ghrelin
Glucagon

- Gonadotropin-releasing hormone **(GnRH)**

- Growth hormone-releasing hormone (GHRH)
Human chorionic gonadotropin (hCG)

- Growth hormone **(GH or hGH)**

- Inhibin

- Insulin

- Insulin-like growth factor (IGF, also somatomedin)
Leptin

- Luteinizing hormone **(LH)**

- Melanocyte stimulating hormone (MSH or ±-MSH)
Neuropeptide Y
Oxytocin
Parathyroid hormone (PTH)
Prolactin (PRL)
Relaxin
Secretin
Somatostatin
Thrombopoietin
Thyroid-stimulating hormone (TSH)
Thyrotropin-releasing hormone (TRH)

Steroid and sterol hormones

Steroidal

- Glucocorticoids
  - Cortisol
- Mineralocorticoids
  - Aldosterone
- Sex steroids
  - Androgens
    - Testosterone
      - Dehydroepiandrosterone (DHEA)
      - Dehydroepiandrosterone sulfate (DHEAS)
      - Androstenedione
    Dihydrotestosterone (DHT)
  - Estrogens
    - Estradiol
    - Progestagen
      - Progesterone
      - Progestins

Sterol

- Vitamin D derivatives
  - Calcitriol

Lipid and phospholipid hormones (eicosanoids)

- Prostaglandins

Leukotrienes
Prostacyclin
Thromboxane

References

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Antiandrogens

An *antiandrogen*, or *androgen antagonist*, is any of a group of hormone receptor antagonist compounds that are capable of preventing or inhibiting the biologic effects of androgens, male sex hormones, on normally responsive tissues in the body (see androgen insensitivity syndrome). Antiandrogens usually work by blocking the appropriate receptors, competing for binding sites on the cell's surface, obstructing the androgens' pathway.

Antiandrogens are often indicated to treat severe male sexual disorders, such as hypersexuality (excessive sexual desire) and sexual deviation, specifically paraphilias, as well as use as an antineoplastic agent and palliative, adjuvant or neoadjuvant hormonal therapy in prostate cancer.

Antiandrogens can also be used for treatment of benign prostatic hyperplasia (prostate enlargement), acne vulgaris, androgenetic alopecia (male pattern baldness), and hirsutism (excessive hairiness). They are also occasionally used as a male contraceptive agent, to purposefully prevent or counteract masculinisation in the case of transwomen undergoing gender reassignment therapy, and to prevent the symptoms associated with reduced testosterone, such as hot flushes, following castration.

The administration of antiandrogens in males can result in slowed or halted development or reversal of male secondary sex characteristics, reduced activity or function of the accessory male sex organs, and hyposexuality (diminished sexual desire or libido).

The term antiandrogen withdrawal response (AAWR) describes the medical course taken when cancer cells adapt to feed on the antiandrogens rather than androgen, so that treatment must be halted in order to starve those cells thriving on the antiandrogens.

Currently available antiandrogen drugs (brand names in parentheses) include:

- Spironolactone (Aldactone, Spiritone), a synthetic 17-spirolactone corticosteroid, which is a renal competitive aldosterone antagonist in a class of pharmaceuticals called potassium-sparing diuretics, used primarily to treat low-renin hypertension, hypokalemia, and Conn's syndrome.
- Cyproterone acetate (Androcur, Climen, Diane 35, Ginette 35), a synthetic steroid, a potent antiandrogen that also possesses progestational properties.
- Flutamide (Eulexin), nilutamide (Anandron, Nilandron) and bicalutamide (Casodex), nonsteroidal, pure antiandrogens. Flutamide is the oldest and has more unwanted side effects than the others. Bicalutamide is the newest and has the least side effects.
- Ketoconazole (Nizoral), an imidazole derivative used as a broad-spectrum antifungal agent effective against a variety of fungal infections, side effects include serious liver damage and reduced levels of androgen from both the testicles and adrenal glands. Ketoconazole is a relatively weak antiandrogen.

- Finasteride (Proscar, Propecia) and dutasteride (Avodart), inhibitors of the 5-±-reductase enzyme that prevent the conversion of testosterone into dihydrotestosterone (DHT). Finasteride blocks only 5-±-reductase type II, dutasteride also blocks type I. They are not general antiandrogens in that they don't counteract the effects or production of other androgens than DHT.

5-alpha-reductase inhibitors

5±-reductase inhibitors (or *5-alpha-reductase inhibitors*) are a group of drugs with antiandrogenic activity, used in the treatment of benign prostatic hyperplasia and androgenic (or androgenetic) alopecia. These drugs decrease the levels of available 5±-reductase prior to testosterone binding with the enzyme, thus reducing levels of dihydrotestosterone that derives from such a bond.

Clinical use

Indications

5±-reductase inhibitors are clinically used in the treatment of conditions which are exacerbated by dihydrotestosterone. Specifically, these indications may include: (Rossi, 2004)

- mild-to-moderate benign prostatic hyperplasia
- androgenic (or androgenetic) alopecia

Adverse drug reactions

Adverse drug reactions (ADRs) experienced with 5±-reductase inhibitors are generally dose-dependent. Common ADRs include impotence, decreased libido, decreased ejaculate volume. Rare ADRs include: breast tenderness and enlargement, and allergic reaction. (Rossi, 2004)

Pharmacology

The enzyme 5±-reductase is involved in the conversion of testosterone to the active form dihydrotestosterone by reducing the ”4,5 double-bond. In benign prostatic hyperplasia, dihydrotestosterone acts as a potent cellular androgen and promotes prostate growth - inhibiting the enzyme reduces the excessive prostate growth. In alopecia, pattern-baldness is one of the effects of androgenic receptor activation. Reducing the levels of dihydrotestosterone thus reduces alopecia.

Examples

- finasteride (Proscar, Propecia)

dutasteride (Avodart)
FCE 28260, an experimental compound

Reference

- Rossi S (Ed.) (2004). Australian Medicines Handbook 2004. Adelaide: Australian Medicines Handbook. ISBN 0-9578521-4-2

GnRH agonists

A *gonadotropin-releasing hormone agonist* (*GnRH agonist*) is a synthetic peptide modeled after the hypothalamic neurohormone GnRH that interacts with its receptor to elicit its biologic response, the release of the pituitary hormones FSH and LH. Agonists do not quickly dissociate from the GnRH receptor. As a result initially there is an increase in FSH and LH

secretion (so-called flare effect), however after about ten days a profound hypogonadal effect is achieved through receptor downregulation. Generally this induced and reversible hypogonadism is the therapeutic goal.

GnRH agonists are synthetically modeled after the natural GnRH decapeptide with specific amino acid substitutions typically in position 6 and 10. These substitutions inhibit rapid degradation. Agonists with 2 substitutions include:

1. leuprolide (Lupron, Eligard),
2. buserelin (Suprefact, Suprecor),
3. nafarelin (Synarel),
4. historelin,
5. goserelin (Zoladex),
6. deslorelin.

Tryptorelin is an agonist with only a single substitution at position 6. Some of these medications are used intranasally, others by injection. Injectables have been formulated for daily, monthly, and quarterly use.

GnRH agonists are useful in:

- Treatment of cancers that are hormonally sensitive and where a hypogonadal state decreases the chances of a recurrence. Thus they are commonly employed in the medical management of prostate cancer and have been used in patients with breast cancer.
- Treatment of delaying puberty in individuals with precocious puberty.
- Management of female disorders that are dependent on estrogen productions. Women with menorrhagia, endometriosis. adenomyosis, or uterine fibroids may receive GnRH agonists to suppress ovarian activity and induce a hypoestrogenic state.
- IVF therapy: they allow for better control of ovarian stimulation during the administration of exohgenous FSH. Typically, after GnRH agonists have induced a state of hypoestrogenism, exogenous FSH is given to stimulate ovarian follicle, followed by human chorionic gonadotropins (hCG) to trigger ovulation.

Side effects of the GnRH agonists are signs and symptoms of hypoestrogenism, including hot flashes, headaches, and osteoporosis. In patients under long-term therapy, small amounts of estrogens could be given back ("add-back regimen") to combat such side effects.

Women of reproductive age who undergo cytotoxic chemotherapy have been pretreated with GnRH agonists to reduce the risk of oocyte loss during such therapy and preserve ovarian function. Further studies are necessary to prove that this approach is useful.

GnRH agonists are pregnancy category X drugs.

Mineralocorticoids

Mineralocorticoids is a class of steroids characterised by their similarity to aldosterone and their influence on salt and water metabolism.

Physiology

The primary endogenous mineralocorticoid is aldosterone, although a number of other endogenous hormones (including Progesterone)and deoxycorticosterone have mineralocorticoid function.

Aldosterone acts on the kidneys to provide active reabsorption of sodium and an associated passive reabsorption of water, as well as, the active secretion of potassium in the principle cells of the cortical collecting tubule and active secretion of protons via proton ATPases in the lumenal membrane of the intercalated cells of the collecting tubule. This in turn results in an increase of blood pressure and blood volume.

Aldosterone is produced in the cortex of the adrenal gland and its secretion is mediated by adrenocorticotrophic hormone (ACTH).

Mode of Action

Mineralocorticoids bind to the cytosolic mineralocorticoid receptor. This type of receptor gets activated upon ligand binding. After a hormone binds to the corresponding receptor, the newly formed receptor-ligand complex translocates itself into the cell nucleus, where it binds to many hormone response elements (HRE) in the promoter region of the target genes in the DNA.

The opposite mechanism is called *transrepression*. The activated hormone receptor interacts with specific transcription factors and prevents the transcription of targeted genes.

Aldosterone and cortisol have similar affinity for the mineralocorticoid receptor however, glucocorticoids circulate at roughly 100 times the level of mineralocorticoids. An enzyme exists in mineralocorticoid target tissues to prevent overstimulation by glucocorticoids. This enzyme, 11-beta hydroxysteroid dehydrogenase type II(Protein:HSD11B2), catalyzes the deactivation of glucocorticoids to 11-dehydro metabolites. Licorice is known to be an inhibitor of this enzyme and chronic consumption can result in a condition known as pseudohyperaldosteronism.

Pathophysiology

Hyperaldosteronism (the syndrome caused by elevated aldosterone) generally results from adrenal neoplasms. The two main resulting problems:

1. Hypertension and edema due to excessive Na+ and water retention.
2. Accelerated excretion of potassium ions. With extreme K+ loss there is muscle weakness and eventually paralysis.

Underproduction, or hypoaldosteronism, leads to the salt-wasting state associated with Addison's disease, although classical congenital adrenal hyperplasia and other disease states may also cause this situation.

Pharmacology

An example of synthetic mineralocorticoids is fludrocortisone (Florinef®). An important mineralocorticoid inhibitor is spironolactone.

Aldosterone

Aldosterone

Aldosterone is a steroid hormone produced by the outer-section (zona glomerulosa) of the adrenal cortex in the adrenal gland to regulate sodium and potassium balance in the blood. It is synthesized from cholesterol by aldosterone synthase, which is absent in other sections of the adrenal gland. It is the sole endogenous member of the class of mineralocorticoids. Acting on mineralocorticoid receptors (MR) on principal cells in the distal tubule of the kidney nephron, it increases the permeability of their apical (luminal) membrane to potassium and sodium and activates their basolateral Na+/K+ pumps, stimulating ATP hydrolysis, reabsorbing sodium (Na+) ions and water into the blood, and excreting potassium (K+) ions into the urine. Aldosterone also stimulates H+ secretion by ±-intercalated cells in the collecting duct, regulating plasma bicarbonate (HCO3) levels and its acid/base balance.[1]

Aldosterone is responsible for the reabsorption of about 2% of filtered sodium in the kidneys, which is nearly equal to the entire sodium content in human blood under normal GFR (glomerular filtration rate).[2]

Unlike neuroreceptors, classic steroid receptors are intracellularly located. The aldosterone/MR receptor complex binds on the DNA to the hormone response element, which alters protein synthesis and the transcription of messenger RNA. Some of the transcribed genes are important for transepithelial sodium transport, including serum and glucocorticoid-induced kinase, channel-inducing factor, K-ras2A, and three subunits of the epithelial sodium channel.

Aldosterone synthesis is stimulated by increased plasma angiotensin II or potassium levels, which are present in proportion to plasma sodium deficiencies. It is also stimulated by plasma acidosis. The secretion of aldosterone has a diurnal rhythm; about 75% of the daily production is secreted between 04:00 am and 10:00 am each day.[3]

Aldesterone release is also stimulated by the stretch receptors located in the atria of the heart. If decreased blood pressure is detected, the adrenal gland is stimulated by these stretch receptors to release aldesterone, which increases sodium reabsorption from the urine, sweat and the gut. This causes increased osmolarity in the extracellular fluid which will eventually return blood pressure toward normal.

Contents

Aldosterone and the kidney

Control of aldosterone release

- The role of the renin-angiotensin system

The role of sympathetic nerves
The role of baroreceptors
The role of the juxtaglomerular apparatus
The plasma concentration of potassium

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3. ^ Hurwitz S, Cohen R, & Williams GH. Diurnal variation of aldosterone and plasma renin activity: timing relation to melatonin and cortisol and consistency after prolonged bed rest. 2004 J Appl Physiol 96: 1406-1414. Full Text

- Williams JS, Williams GH. 50th anniversary of aldosterone. J Clin Endocrinol Metab. 2003 Jun;88(6):2364-72. Full text. PMID 12788829.

Selective estrogen receptor modulator

Selective estrogen receptor modulators (*SERMs*) is a class of medication that acts on the estrogen receptor. A characteristic that distinguishes these substances from receptor agonists and antagonists is that their action is different for various tissues, thereby granting the possibility to selectively inhibit or stimulate estrogen-like action in various tissues.

Members

Members are:

- clomifene
- Raloxifene
- Tamoxifen
- toremifene

bazedoxifene
lasofoxifene
ormeloxifene

Uses

SERMs are used dependent on their pattern of action in various tissues:

- clomifene is used in anovulation
- Raloxifene is used for osteoporosis and is being studied as a breast cancer preventative
- Tamoxifen and toremifene are used for breast cancer
- ormeloxifene is used for contraception

Some SERMs may be good replacements for hormone replacement therapy (HRT), which recent studies have called into question, although the above agents still have an unacceptably high risk of thrombosis and other side-effects to allow for widespread use.

Method of action

Although the SERMs have no immediate structural relationship with 17^2-estradiol, they are stereochemically similar to this estrogen.

There are three types of estrogen receptors, which are intracellular: ± (± homodimer), ^{2} (^{2} homodimer) and ±^{2} (±- and ^{2}-receptor heterodimer). Different tissues have more or less of each class. In turn, each SERM has more affinity to one and less to the other estrogen receptor isoform. The ±-receptor is generally stimulatory, but the ^{2}-receptor may inhibit the ±-isoform as well as suppressing transcription independently.

Genes activated or suppressed by estrogen receptors generally have an estrogen response element sequence in their promotor.

Some SERMs, through this process, also augment the transcription of coactivator molecules, which may be indispensable for their pharmacological action.

Actions

The actions of SERMs on various tissues:

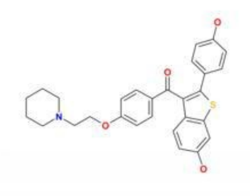
- Pituitary gland - clomifene blocks estrogen action, leading to an increase of follicle-stimulating hormone.
Uterus - tamoxifen may increase endometrial carcinoma risk, but raloxifene does not. Data on toremifene and clomifene is insufficient.
Breast - all SERMs decrease breast cancer risk, and tamoxifen is mainly used for its ability to inhibit growth in estrogen receptor-positive breast cancer.

Deep venous thrombosis - the risk may be elevated in all SERMs. Cholesterol and triglycerides - levels respond favorably to SERMs. Bone turnover and postmenopausal osteoporosis respond favorably to SERMs. Hot flashes are increased by all SERMs.

References

- Riggs BL, Hartmann LC. Selective estrogen-receptor modulators - mechanisms of action and application to clinical practice. N Engl J Med 2003;348:618-29. PMID 12584371.

Raloxifene



Systematic (IUPAC) name

[6-hydroxy-2-(4-hydroxyphenyl)- benzothiophen-3-yl]- [4-[2-(1-piperidyl)ethoxy]phenyl] -methanone

Identifiers

CAS number rn=1" href="http://www.nlm.nih.gov/cgi/mesh/2006/MB_cgi?term=84449-90-1&rn=1"> 84449-90-1

ATC code G03**XC01**

PubChem 5035

DrugBank APRD00400

Chemical data

Formula $C_{28}H_{27}NO_4S$

Mol. weight 473.584 g/mol

Pharmacokinetic data

Bioavailability **2%**

Protein binding 95%

Metabolism Hepatic glucuronidation, CYP system not involved

Half life 27.7 hours

Excretion Fecal

Therapeutic considerations

Pregnancy cat. $X_{(AU)}$ $X_{(US)}$

Legal status P*rescription only*

Routes Oral

Raloxifene is an oral selective estrogen receptor modulator which is used in the prevention of osteoporosis in postmenopausal women. It was announced on April 17, 2006, that raloxifene is as effective as tamoxifen in reducing the incidence of breast cancer in certain high risk groups of females, [1] [2] though with a reduced risk of thromboembolic events and cataracts in patients taking raloxifene versus those taking tamoxifen.[1] It has not been approved by the FDA for this use, and there has been criticism in the mainstream oncology press of the way that the information was released.[2] There has been some confusion in the lay media about the meaning of the trial results. There is no specific clinical evidence for the use of raloxifene in the adjuvant treatment of breast cancer over established drugs such as tamoxifen or anastrozole.

Raloxifene is produced by Eli Lilly Pharmaceuticals and is sold under the brand name *Evista®*.

SERMs mimic estrogen in some tissues and have anti-estrogen activity in others. Other SERMs, such as Pfizer's lasofoxifene and Wyeth's bazedoxifene are in the late stages of clinical development.

Description

Raloxifene hydrochloride (HCl) has the empirical formula $C_{28}H_{27}NO_4S \bullet HCl$, which corresponds to a molecular weight of 510.05 g/mol. Raloxifene HCl is an off-white to pale-yellow solid that is very slightly soluble in water.

Indication

Raloxifene is indicated for the treatment and prevention of osteoporosis in postmenopausal women.

For either osteoporosis treatment or prevention, supplemental calcium and/or vitamin D should be added to the diet if daily intake is inadequate.

Recently it was shown that raloxifene is a very potent drug for prevention of breast cancer. In a recent clinical trial, the drug was shown to be as effective as tamoxifen for breast cancer prevention with lesser side effects[3].

Contraindications and Precautions

Raloxifene is contraindicated in lactating women or women who are or may become pregnant, in women with active or past history of venous thromboembolic events, including deep vein thrombosis, pulmonary embolism, and retinal vein thrombosis and in women known to be hypersensitive to raloxifene.

Adverse Reactions

Common adverse events considered to be drug-related were hot flashes and leg cramps.

Raloxifene may infrequently cause serious blood clots to form in the legs, lungs, or eyes. Other reactions experienced include leg swelling/pain, trouble breathing, chest pain, vision changes. Eli Lilly, the manufacturer of raloxifene, recently issued a warning that use of raloxifene may be associated with increased risk of death from stroke

References

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2. ^ (2006) "A STARring role for raloxifene?". Lancet Oncol *7* (6): 443. PMID 16750489.

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Tamoxifen

Systematic (IUPAC) name

(Z)-2-[4-(1,2-diphenylbut-1-enyl)phenoxy]-N,N-dimethyl-ethanamine

Identifiers

CAS number rn=1" href="http://www.nlm.nih.gov/cgi/mesh/2006/MB_cgi?term=10540-29-1&rn=1"> 10540-29-1

ATC code L02**BA01**

PubChem 5376

DrugBank APRD00123

Chemical data

Formula $C_{26}H_{29}N$

Mol. weight 371.515 g/mol, 563.638 g/mol (citrate salt)

Pharmacokinetic data

Metabolism Hepatic (CYP3A4, 2C9 and 2D6)

Half life 5-7 days

Excretion Fecal

Therapeutic considerations

Pregnancy cat. B3 $_{(Au)}$ D $_{(US)}$

Legal status POM$_{(UK)}$ $_{\text{-only}(US)}$

Routes Oral

Tamoxifen is an oral selective estrogen receptor modulator which is used in breast cancer treatment, and is currently the world's largest selling breast cancer treatment. It is used for the treatment of early and advanced breast cancer in pre- and post-menopausal women. It is also approved by the Food and Drug Administration (FDA) for the reduction of the incidence of breast cancer in women at high risk of developing the disease. It has been further approved for the reduction of contralateral (in the opposite breast) breast cancer.

Tamoxifen competes with oestrogen in the body for oestrogen receptors in breast tissue so that transcription of oestrogen-responsive genes is inhibited.

Tamoxifen was invented by ICI Pharmaceuticals (now AstraZeneca) and is sold under the brand names *Nolvadex*, *Istubal*, and *Valodex*. It is also available as a generic drug in a number of countries. In the United States and other countries, Tamoxifen was almost always referred to by its generic name even before its patents expired.

A rare condition occasionally treated with tamoxifen is retroperitoneal fibrosis.

Tamoxifen is sometimes used to treat gynecomastia in men. Tamoxifen is also used by bodybuilders in a steroid cycle to try and prevent or reduce drug-induced gynecomastia caused by steroids that are used in the same cycle.

Tamoxifen is also used to treat infertility in women with anovulatory disorders. A dose of 10-40 mg per day is administered in days 3-7 of a woman's cycle.

On April 17, 2006, it was announced that Raloxifene is equally effective in reducing the incidence of breast cancer, but caused fewer side effects.

Side effects

Tamoxifen is a selective estrogen receptor modulator. Even though it is an antagonist in breast tissue it acts as partial agonist on the endometrium. Therefore endometrial changes, including cancer, are among tamoxifen's side effects. Source: Golan et al. Principles of Pharmacology page 450. For some women, tamoxifen can cause a rapid increase in triglyceride concentration in the blood. In addition there is an increased risk of thromboembolism especially during and immediately after major surgery or periods of immobility.

4-hydroxytamoxifen

4-hydroxytamoxifen is a form of the drug tamoxifen that is made by the body after taking tamoxifen. It can also be made in the laboratory, and may help decrease breast density. A topical form of 4-hydroxytamoxifen is being studied in breast cancer screening.

Pharmacogenetics

Patients with variant forms of the gene CYP2D6 (also called simply 2D6) may not receive full benefit from tamoxifen. On Oct 18, 2006 the Subcommittee for Clinical Pharmacology recommended relabeling tamoxifen to include information about this gene in the package insert.

Sex steroids

Sex steroids, also known as *gonadal steroids*, are steroid hormones which interact with vertebrate androgen or estrogen receptors. Natural sex steroids are made by the gonads (ovaries or testes), by adrenal glands, or by conversion from other sex steroids in other tissues such as liver or fat. The term *sex hormone* nearly always is synonymous with sex steroid.

Sex steroids play important roles inducing the body changes known as primary sex characteristics and secondary sex characteristics.

The development of both primary and secondary sexual characteristics is controlled by sex hormones after the initial fetal stage where the presence or absence of the Y-chromosome and/or the SRY gene determine development.

In many contexts, the two main classes of sex steroids are androgens and estrogens, of which the most important human examples are testosterone and estradiol respectively. Other contexts will include Progestagen as a third class of sex steroids, distinct from androgens and estrogens. Progesterone is the most important and only naturally occurring human progestagen.

There are also many synthetic sex steroids. Synthetic androgens are often referred to as anabolic steroids. Synthetic estrogens and progestins are used in oral contraceptive pills. Diethylstilbestrol (DES) is a synthetic estrogen.

Sex steroids include:

- androgens**:xx**
  - testosterone
    - androstenedione
  dihydrotestosterone
    - Dehydroepiandrosterone
  - anabolic steroids
- estrogens**:**
  - estradiol
    - diethylstilbestrol
  - Progestagen:
    - Progesterone
    - progestins

Androgens

Androgen is the generic term for any natural or synthetic compound, usually a steroid hormone, that stimulates or controls the development and maintenance of masculine characteristics in vertebrates by binding to androgen receptors. This includes the activity of the accessory male sex organs and development of male secondary sex characteristics. Androgens, which were first discovered in 1936, are also called *androgenic hormones* or *testoids*. Androgens are also the original anabolic steroids. They are also the precursor of all estrogens, the female sex hormones. The primary and most well-known androgen is testosterone.

Types of androgens

A subset of androgens, *adrenal androgens*, includes any of the 19-carbon steroids synthesized by the adrenal cortex, the outer portion of the adrenal gland, that function as weak steroids or steroid precursors, including Dehydroepiandrosterone (DHEA), dehydroepiandrosterone sulfate (DHEA-S), and androstenedione.

Besides testosterone, other androgens include:

- Dehydroepiandrosterone (DHEA): a steroid hormone produced from cholesterol in the adrenal cortex, which is the primary precursor of natural estrogens. DHEA is also called dehydroisoandrosterone or dehydroandrosterone.
- Androstenedione (Andro): an androgenic steroid, which is produced by the testes, adrenal cortex, and ovaries. While androstenediones are converted metabolically to testosterone and other androgens, they are also the parent structure of estrone. Use of androstenedione as an athletic or body building supplement has been banned by the International Olympic Committee as well as other sporting organizations.
- Androstenediol: the steroid metabolite that is thought to act as the main regulator of gonadotropin secretion.
- Androsterone: a chemical by-product created during the breakdown of androgens, or derived from Progesterone, that also exerts minor masculinising effects, but with one-seventh the intensity of testosterone. It is found in approximately equal amounts in the plasma and urine of both males and females.
- Dihydrotestosterone (DHT): a metabolite of testosterone that is actually a more potent androgen in that it binds more strongly to androgen receptors.

Androgen functions

Development of the male

During mammalian development, the gonads are at first capable of becoming either ovaries or testes[1]. In humans, starting at about week 4 the gonadal rudiments are present within intermediate mesoderm adjacent to the developing kidneys. At about week 6, epithelial sex cords develop within the forming testes and incorporate the germ cells as they migrate into the gonads. In males, certain Y chromosome genes, particularly SRY, control development of the male phenotype, including conversion of the early bipotential gonad into testes. In males, the sex cords fully invade the developing gonads.

By week 8 of human fetal development, Leydig cells appear in the differentiating gonads of males. The mesoderm-derived epithelial cells of the sex cords in developing testes become the Sertoli cells which will function to support sperm cell formation. A minor population of non-epithelial cells exists between the tubules, these are the androgen-producing Leydig cells. The Leydig cells can be viewed as producers of androgens that function as paracrine hormones required by the Sertoli cells in order to support sperm production. Soon after they differentiate, Leydig cells begin to produce androgens which are required for masculinization of the developing male fetus (including penis and scrotum formation). Under the influence of androgens, remnants of the mesonephron, the Wolffian ducts, develop into the epididymis, vas deferens and seminal vesicles. This action of androgens is supported by a hormone from Sertoli cells, AMH, which prevents the embryonic Müllerian ducts from developing into fallopian tubes and other female reproductive tract tissues in male embryos. AMH and androgens cooperate to allow for the normal movement of testes into the scrotum.

Before the production of the pituitary hormone LH by the embryo starting at about weeks 11-12, human chorionic gonadotrophin (hCG) promotes the differentiation of Leydig cells and their production of androgens. Androgen action in target tissues often involves conversion of testosterone to 5±-dihydrotestosterone (DHT).

Spermatogenesis

During puberty, androgen, LH and FSH production increase and the sex cords hollow out, forming the seminiferous tubules, and the germ cells start to differentiate into sperm. Throughout adulthood, androgens and FSH cooperatively act on Sertoli cells in the testes to support sperm production[2]. Exogenous androgen supplements can be used as a male contraceptive. Elevated androgen levels caused by use of androgen supplements can inhibit production of LH and block production of endogenous androgens by Leydig cells. Without the locally high levels of androgens in testes due to androgen production by Leydig cells, the seminiferous tubules can degenerate resulting in infertility.

Inhibition of fat deposition

Males typically have less adipose tissue than females. Recent results indicate that androgens inhibit the ability of some fat cells to store lipids by blocking a signal transduction pathway that normally supports adipocyte function[3].

Muscle mass

Males typically have more skeletal muscle mass than females. Androgens promote the enlargement of skeletal muscle cells and probably act in a coordinated manner to enhance muscle function by acting on several cell types in skeletal muscle tissue[4].

Brain

Circulating levels of androgens can influence human behavior because some neurons are sensitive to steroid hormones. Androgen levels have been implicated in the regulation of human aggression[5] and libido.

Insensitivity to androgen in humans

Reduced ability of a XY karyotype fetus to respond to androgens can result in one of several problems, including infertility and several forms of intersex conditions.

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4. ^ Androgen Receptor in Human Skeletal Muscle and Cultured Muscle Satellite Cells: Up-Regulation by Androgen Treatment by Indrani Sinha-Hikim, Wayne E. Taylor, Nestor F. Gonzalez-Cadavid, Wei Zheng and Shalender Bhasin in The Journal of Clinical Endocrinology & Metabolism (2004) volume 89 pages 5245-5255.

5. ^ Full text article available in PDF format: "Testosterone and aggressiveness" by Marco Giammanco, Garden Tabacchi, Santo Giammanco, Danila Di Majo and Maurizio La Guardia in Endocrinology (2005) Entrez PubMed 16210377

See also

- antiandrogen

Anabolic steroids

Anabolic androgenic steroids (AAS) are a class of natural and synthetic steroid hormones that promote cell growth and division, resulting in growth of several types of tissues, especially muscle and bone. Different anabolic androgenic steroids have varying combinations of androgenic and anabolic properties, and are often referred to in medical texts as AAS (anabolic/androgenic steroids). Anabolism is the metabolic process that builds larger molecules from smaller ones.

Anabolic steroids were first discovered in the early 1930s and have since been used for numerous medical purposes including stimulation of bone growth, appetite, puberty, and muscle growth. The most wide spread use of anabolic steroids is their use for chronic wasting conditions including cancer and AIDS. Anabolic steroids can produce numerous physiological effects including increased protein synthesis, muscle mass, strength, appetite and bone growth. Anabolic steroids have also been associated with numerous side effects when administered in excessive doses and these include elevated cholesterol (increase in LDL, decreased HDL levels), acne, elevated blood pressure, hepatotoxicity, and alterations in left ventricle morphology.

Today anabolic steroids are controversial because of their widespread use in numerous sports and their purported side effects. While there are numerous health issues associated with excessive anabolic steroid use, there is also a substantial amount of propaganda, junk science and misconceptions concerning their use. Anabolic steroids are controlled in a few countries including the United States where they are listed as Schedule III in the Controlled Substances Act as well as Canada and Britain who also have laws controlling their use and distribution.

Anabolic and virilizing effects

Anabolic androgenic steroids produce both anabolic and virilization (also known as androgenic) effects. Most anabolic steroids work in two simultaneous ways. First, they work by binding the androgen receptor and increasing protein synthesis. Second, they also reduce recovery time by blocking the effects of the stress hormone, cortisol, on muscle tissue. As a result, catabolism of the body's muscle mass is greatly reduced.

Examples of anabolic effects:

- Increased protein synthesis from amino acids
Increased muscle mass and strength[1][2][3]
Increased appetite
Increased bone remodeling and growth
Stimulation of bone marrow increasing production of red blood cells

Examples of virilizing/androgenic effects:

- Growth of the clitoris (clitoral hypertrophy) in females and the penis in male children (the adult penis does not grow indefinitely even when exposed to high doses of androgens)
Increased growth of androgen-sensitive hair (pubic, beard, chest, and limb hair)
Increased vocal cord size, deepening the voice
Increased libido
Suppression of endogenous sex hormones
Impaired spermatogenesis

Possible unwanted side effects

Many androgens are capable of being metabolized to compounds which can interact with other steroid hormone receptors including the estrogen, progesterone, and glucocorticoid receptors, producing additional (usually) unwanted effects:

- Possible elevated blood pressure
Cholesterol levels –Some steroids can cause a increase in LDL, Decreased HDL levels[4]. This can cause a increase in risk of cardiovascular disease[5] or coronary artery disease[6] in men with high risk of bad cholesterol.
Acne– Due to the stimulation of sebaceous gland[7][8]
Conversion to DHT (Dihydrotestosterone). This can accelerate or cause premature baldness and prostate cancer.
Altered left ventricle morphology – AAS can induce an unfavourable

enlargement and thickening of the left ventricle, which loses its diastolic properties with the mass increase.[9] However the negative relation of left ventricle morphology to decreased cardiac function has been disputed.[10] Hepatotoxicity – Caused particularly by oral anabolic steroid compounds which are 17-alpha-alkylated in order to not be destroyed by the digestive system. Gingival overgrowth - AAS is closely associated with significant levels of gingival enlargement.[11]

Male-specific side effects

- Gynecomastia – Breast development in males. It is usually due to high levels of circulating estrogen. These high levels are the result of the increased level of conversion of testosterone to estrogen via the aromatase enzyme. Reduced sexual function and temporary infertility[12][13][14] Testicular atrophy – Temporary side effect that is due to decreases in natural testosterone levels inhibiting spermatogenesis. As most of the mass of the testes is developing sperm, the size of the testicles usually returns to normal within a few weeks of discontinuing anabolic steroid use when spermatogenesis resumes.[15]

Female-specific side effects

- Body hair increase

Deepening of the voice
Enlarged clitoris (clitoral hypertrophy)
Temporary decrease in menstrual cycles

Adolescent-specific side effects

- Stunted growth – Abuse of the agents may prematurely stop the lengthening of bones (premature epiphyseal fusion through increased estrogen)

Accelerated bone maturation
Slight beard growth

An ideal anabolic steroid (a hormone with purely anabolic effects and no virilizing or other side effects) has been widely sought. Many synthetic anabolic steroids have been developed in an attempt to find molecules that produced a higher degree of anabolic rather than virilizing effects. Unfortunately, the most effective steroids known for increasing lean body mass also have the strongest androgenic characteristics.

Medical uses

Anabolic steroids were tried by physicians for many purposes from the discovery of synthetic testosterone in the 1930s to the 1950s with varying success. One of the initial medical uses of steroids was treatment of chronic wasting, such as was experienced by Nazi

concentration camp prisoners and prisoners of war. During World War II, German scientists worked on synthesizing other anabolic steroids, and ran experiments on human prisoners, as well as with their own soldiers. They had hoped to increase the aggressive tendencies of their troops. Adolf Hitler's own physician reported that Hitler had been given testosterone derivative injections to treat various ailments.[16]

- Bone marrow stimulation: For decades, anabolic steroids were the mainstay of therapy for hypoplastic anemias not due to nutrient deficiency, especially aplastic anemia. Anabolic steroids are slowly being replaced by synthetic protein hormones (such as epoetin alfa) that selectively stimulate growth of blood cell precursors.
- Growth stimulation: Anabolic steroids were used heavily by pediatric endocrinologists for children with growth failure from the 1960s through the 1980s. Availability of synthetic growth hormone and increasing social stigmatization of anabolic steroids led to discontinuation of this use. Stimulation of appetite and preservation and increase of muscle mass: Anabolic steroids have been given to people with chronic wasting conditions such as cancer and AIDS.[17][18]
- Induction of male puberty: Androgens are given to many boys distressed about extreme delay of puberty. Testosterone is now nearly the only androgen used for this purpose but synthetic anabolic steroids were often used prior to the 1980s.
- Testosterone enanthate may prove to be a useful, safe, reversible, effective method of male hormonal contraception in the near future.[19][20]
- Used for age related problems in elderly people. Anabolic Steroids have been shown to help in many age related problems in the elderly.[21]
- Used in hormone replacement therapy for men with low levels of testosterone. (see hypogonadism)
- Used for gender dysmorphia: whereby secondary male characteristics (puberty) are initiated in female-to-male diagnosed patients. Most commonly used testosterone derivatives are Sustanon and Testosterone Enanthate which cause the voice to deepen, increased bone and muscle mass, facial hair, increased levels of red blood cells and clitoral enlargement.

Administration

Medical Disclaimer

There are two common routes for the administration of anabolic steroids: oral (for steroids in pill form) and injectable (this category includes both oil-dissolved and water-dissolved steroids.) Also, transdermal (through the skin) administration via cremes or transdermal patches has become popular in the last several years.

Anabolic steroids should *never* be injected by persons unfamiliar with safe injection sites and practices or without first consulting a doctor. Injectable steroids are commonly injected IM (intramuscularly) with 1-1.5" 18-25 gauge needles. Care must be taken to maintain

cleanliness when injecting. Infection and disease can result if careless procedures are used. Care must also be taken when selecting an injection site. Injections into nerves will be extremely painful and dangerous. Injection into vessels is dangerous as well, as this can cause an embolism or other complications. Common injection sites include the shoulders, outer thighs, and buttocks. Note however, that the sciatic nerve runs right up the back of each leg and up the middle of both buttocks. The triceps, biceps and latissumus dorsi also have been used, however, this practice can be dangerous. Blood vessels are abundant in these and other areas. Common amounts used at any one time are typically on the order of a few tens of mg/day for oral steroids, to several hundred mg/week for injectable steroids. As with any drug, increasing the dosage increases the risk of the above side effects.

Use and abuse in sports

Anabolic steroids have been used by men and women in many different kinds of professional sports (track and field, weightlifting, bodybuilding, shot put, cycling, baseball, wrestling, mixed martial arts, boxing, football, etc.) to attain a competitive edge or to assist in recovery from injury. Steroid use to obtain competitive advantage is prohibited by the rules of the governing bodies of many sports. However, steroids are also used by many non-professional athletes to enhance physical performance, and are also widely used by amateur bodybuilders to enhance physical appearance. Unfortunately, these powerful compounds are also used by adolescents.

According to the 1999 Monitoring the Future study, the percentage of eighth, tenth, and twelfth graders in the United States who reported using steroids at least once in their lives increased steadily over the preceding four years (an average of 1.8% in 1996, 2.1% in 1997, 2.3% in 1998, and 2.8% in 1999). In addition, steroid use to enhance athletic performance is no longer limited to high school males: a 1998 Pennsylvania State University study found that 175,000 high school girls nationwide reported taking steroids at least once in their lifetime. The National Institute on Drug Abuse found that 3.4% of all high school seniors report using steroids at least once in 2005. Nearly 2% of 8th graders admitted to using steroids.

Minimizing the side effects

Typically, bodybuilders, athletes and sportsmen who use anabolic steroids try to minimize the negative side effects. For example, users may increase their amount of cardiovascular exercise to help negate the effects of left ventricle hypertrophy.

Some androgens will aromatise and convert to estrogen, potentially causing some combination of the side effects listed above. During a steroid cycle users may take an aromatase inhibitor and/or a SERM; these drugs affect aromatisation and estrogen receptor binding respectively. The SERM tamoxifen, is of particular interest as it prevents binding to the estrogen receptor in the breast, reducing the risk of gynecomastia.[22]

Furthermore, to combat the natural testosterone suppression and to restore proper HPTA function, what is known as 'post-cycle therapy' (PCT) is self prescribed. PCT takes place after the course of anabolic steroids. It typically consists of a combination of the following drugs, depending on which protocol is used:

- A SERM such as clomiphene citrate and/or tamoxifen citrate (this is the primary PCT drug).

An aromatase inhibitor such as anastrozole.

Human chorionic gonadotropin, hCG (this has become less common as it is now more often used throughout the cycle rather than after).

The aim of PCT is to return the body's endogenous hormonal balance to its original state within the shortest space of time.

Those prone to premature hair loss due to steroid use have been known to take the prescription drug finasteride for prolonged periods of time. Finasteride reduces the conversion of testosterone to DHT, the latter having much higher potency for alopecia. Finasteride is useless in the cases when steroid is not converted into a more androgenic derivative. Finasteride is also used as a masking agent by those who are subject to steroid testing.

Since anabolic steroids can be toxic to the liver or can cause increases in blood pressure or cholesterol, many users consider it ideal get frequent blood work tests and blood pressure tests to make sure their blood pressure or cholesterol are still within normal levels. Since anabolic steroids can increase cholesterol they increase the risk for heart attack in users.[23] So it is generally considered mandatory for all users to get blood work while using anabolic steroids.

Popular misconceptions

Anabolic steroids, like many other drugs, have been at the center of a lot of controversy and because of this there are many popular misconceptions and myths concerning their purported effects and side effects. As with many infamous drugs in popular culture, the misconceptions relating to anabolic steroids have likely arisen from misunderstandings of actual side effects of anabolic steroids. One such example might include the myth that anabolic steroids can ‘shrink’ one's penis. It is likely that this myth came from the real side effect of anabolic steroids known as testicular atrophy, in which the use of anabolic steroids causes reduced secretion of the gonadotropins luteinizing hormone and follicle stimulating hormone from the anterior pituitary, thus reducing testicle size. This side effect is temporary and the testicles return to normal soon after exogenous androgen administration is halted.[24]

Another common misconception purveyed in popular culture and the media include the myth that anabolic steroids are highly dangerous and users' mortality rates are high. Anabolic steroids are used widely in the medical field without any serious health risks to users[25][26][27], and no scientific evidence has shown any long-term serious health defects from correct use of anabolic steroids. While risk of death is present in many drugs, the risk of premature death from use of anabolic steroids seems to be extremely low.[28] It is possible this myth gained popularity from claims that Lyle Alzado died from brain cancer caused by anabolic steroids. Alzado himself had claimed that his cancer was caused by anabolic steroids. However, there is no medical evidence anabolic steroids can cause brain cancer and Alzado's own doctors admitted anabolic steroids had nothing to do with his death.[29]

More myths relating to purported side effects include claims that anabolic steroids have caused many teenagers to commit suicide. While lower levels of testosterone have been known to cause depression, and ending a steroid cycle is known to result in temporarily lower testosterone levels, the claim that anabolic steroids are responsible for specific suicides among teenagers is highly questionable. In the United States the estimated use of anabolic steroids among high school students was 2.8% in 1999. On the other hand, in the year 2000 in the United States, suicide was the third leading cause of death among 15- to 24-year-olds.[30] With the suicide rate this high among teenagers, concluding anabolic steroids are responsible for the suicides of teenagers who happened to be taking them prior to committing suicide is a Post hoc logical fallacy. Also, even though teen bodybuilders have been using steroids since at least the early 1960s, only a few cases suggesting a link between steroids and suicide have been reported in the medical literature.[31]

One of the most common misconceptions regarding the side effects of anabolic steroids is known as ‘roid rage’. There seems to be little or no evidence such a condition actually exists. Most studies done on "angry behavior" and anabolic steroid use show no psychological effect, implying that either "roid rage" doesn't exist or that anabolic steroids' effects on aggression are too small to be measured. Many scientists and medical professionals conclude anabolic steroids have no real effect on increased angry behavior.[32][33][34][35][36]

Arnold Schwarzenegger is the target of yet another myth regarding the purported side effects of anabolic steroids. Arnold Schwarzenegger has admitted to using anabolic steroids during his bodybuilding career for many years[37], and in 1997 he went in for surgery to correct a defect relating to his heart. Some have assumed this was due to anabolic steroids. However, Arnold Schwarzenegger was born with a congenital genetic defect in which his heart had a bicuspid aortic valve — in other words, whereas normal hearts have three cusps, his had only two, which can occasionally cause problems later in life.[38]

Illegal trade in anabolic steroids

Since anabolic steroids are often produced in different countries than in which they are distributed, they must be smuggled across international borders. Like most significant smuggling operations, sophisticated organized crime is involved, often in conjunction with other smuggling efforts (including other illegal drugs). Unlike psychoactive recreational drugs such as cannabis and heroin, there have not been many high profile cases of individual smugglers of anabolic steroids being caught. The majority of those using illegally obtain the drugs via this black market,[39][40] and more specifically, pharmacists, veterinarians, and physicians. Anabolic Steroids purchased through the Black Market may be counterfeit, or originally manufactured for veterinary applications. Which in and of itself isn't dangerous except for the fact they are sometimes produced and handled in cruder and less sterile environments.[41][42]

Production

Anabolic steroids need sophisticated pharmaceutical processes and equipment to produce, so they are produced by legitimate pharmaceutical companies or underground laboratories with large overheads. Common problems associated with illegal drug trades, such as chemical substitutions, cutting, and diluting, affect illegal anabolic steroids such that when it reaches distribution the quality may be questionable or possibly dangerous.

In the 1990s most US producers such as Ciba, Searle and Syntex stopped making and marketing anabolic steroids within the US. However, in many other regions, particularly Eastern Europe, they are still produced in quantity. European anabolic steroids are the source of most medical grade anabolic steroids sold illegally in North America. However, anabolic steroids are still in wider use for veterinary purposes, and many illegal anabolic steroids are actually veterinary grade.

Distribution

In the United States and Canada, steroids are purchased just like any illegal drug through dealers who are able to obtain the drugs from a number of sources, although most users would prefer to buy from legitimate sources but cannot because of the restrictive laws against steroid possession. Counterfeit steroids are a common solution to the lack of legal availability in the United States and Canada, although black-market importation continues from Mexico, Thailand and other countries where steroids are more easily available and, in many countries, not illegal at all. Many people produce fake steroids and attempt to sell them over the internet which causes a wide variety of health concerns.

Most illicit anabolic steroids are now sold at gyms, competitions, and through the mail. For the most part, these substances are smuggled into the United States. In addition, a significant number of counterfeit products are sold as anabolic steroids, particularly via mail order from websites posing as overseas pharmacies. In addition to the recreational use of anabolic steroids, users in Great Britain have been shown to consume illicit drugs as well, such as cannabis, and cocaine.[39][43][44]

History

Comments on professional athletes in ancient Greece suggest that a wide variety of natural steroidal substances were used to promote androgenic and anabolic growth. These may have ranged from testicular extracts to plant materials. Traditional medicine in general, in the West as well as in contemporary Asian medicine, has a wide pharmacopeia of substances intended to promote virility and masculine traits, though not entirely oriented towards muscle growth and athletic ability so much as sexual performance. In Chinese traditional medicine, substances such as deer antler, tiger bone, bear gall bladder, ginseng and other roots and much more are all primarily consumed and were thought to bolster the male organism. There is no science behind these claims.

Modern pharmaceutical anabolic steroids are believed to have been inadvertently discovered by German scientists in the early 1930s, but at the time the discovery was not considered significant enough to warrant further study. The first known reference to an anabolic steroid in a US weightlifting/bodybuilding magazine is testosterone propinate in a

letter to the editor in Strength and Health magazine in 1938. In the 1950s, scientific interest was rekindled, and methandrostenolone (Dianabol) was approved for use in the United States by the federal Food and Drug Administration in 1958 after promising trials had been conducted in other countries.

Throughout the '50s, '60s, '70s and even '80s there was doubt Anabolic Steroids even had a real effect. In a 1972 study,[45] participants were informed they would receive injections of anabolic steroids on a daily basis, but instead had actually been give placebo. They reportedly could not tell the difference, and the perceived performance enhancement was similar to that of subjects taking the real anabolic compounds. This study had many flaws including inconsistent controls and insignificant doses. According to Geraline Lin, a researcher for the National Institute on Drug Abuse, at the time of the books' publishing in 1996, the results of the study remained unchallenged for 18 years.[46]

In the 1996 study mentioned above which was founded by the NIH it examined the effect of high doses of testosterone enanthate (600 mg/week intramuscularly for 10 weeks). The results showed a clear increase in muscle mass and decrease in fat mass in those who took the testosterone opposed to the placebo. No adverse reactions were noted.[33]

The U.S. Congress in the Anabolic Steroid Control Act of 1990 placed anabolic steroids into Schedule III of the Controlled Substances Act (CSA). The CSA defines anabolic steroids as any drug or hormonal substance chemically and pharmacologically related to testosterone (other than estrogens, progestins, and corticosteroids) that promotes muscle growth.

By the early 1990s after anabolic steroids were scheduled in the United States several pharmaceutical companies stopped manufacturing or marketing the products in the United States, including Ciba, Searle, Syntex and others.

In addition, an entire market for counterfeit drugs emerged at this time. Never seen in the previous 30 years of their availability on the U.S. market, computers and scanning technology made the ease of counterfeiting legitimate products by utilizing their original label design, and the market was flooded with products that contained everything from mere vegetable oil to toxic substances which unsuspecting users injected into themselves, of which some died as a result of blood poisoning, methanol poisoning or subcutaneous abscess.

On January 20, 2005, the Anabolic Steroid Control Act of 2004 took effect, amending the Controlled Substance Act to place both anabolic steroids and prohormones on a list of controlled substances, making possession of the banned substances without a prescription a federal crime.[47]

Movement for decriminalization

Anabolic steroids are Schedule III controlled substances in the United States and are strictly regulated in some other countries. (It is perhaps worth noting that anabolic steroids are readily available without a prescription in some other countries such as Mexico, Germany, and Thailand.) However, since the U.S. Congress passed the Anabolic Steroid Control Act of 1990, a small movement has arisen that is highly critical of current laws concerning anabolic steroids. On June 21, 2005 Real Sports aired a segment discussing the legality and prohibition of anabolic steroids in America.[48] The show featured Dr. Gary Wadler, chairman of the U.S. Anti- Doping Agency and a prominent anti-steroid activist. When pressed for scientific evidence by correspondent Armen Keteyian that anabolic

steroids are as 'highly fatal' as he claims, Wadler admitted there was no evidence. Gumbel concluded the 'hoopla' concerning the dangers of anabolic steroids in the media was 'all smoke and no fire.' The show also featured John Romano, a pro-steroid activist who authors 'The Romano Factor,' a pro-steroid column for bodybuilding magazine Muscular Development.[49]

In July 2005 Philip Sweitzer, an Attorney and Author, published an open letter to the Members of the House Committee on Government Reform, and the Senate Committee on Commerce et al. In it he criticized lawmakers' actions in scheduling anabolic steroids, as well as criticized their 'disregard of scientific reality for symbolic effect.' He also pleaded for the consideration of the decriminalization of anabolic steroids and asked for a new policy direction.[50] The U.S. government's position since the late 1980's has been and continues to be that the risks of steroid use are too great to allow them to be decriminalized or unregulated.

List of anabolic compounds commonly used as ergogenic aids

- Testosterone (attached to various esters enanthate, cypionate, propinate or suspended in oil or water)

Methandrostenolone / methandienone (Dianabol)
Nandrolone Decanoate (Deca-durabolin)
Nandrolone Phenylpropionate (Durabolin)
Boldenone Undecylenate (Equipoise)
Stanozolol (Winstrol)
Oxymetholone (Anadrol-50)
Oxandrolone (Anavar)
Fluoxymesterone (Halotestin)
Trenbolone (Fina)
Methenolone Enanthate (Primobolan)
4-chlordehydromethyltestosterone (Turinabol)
Mesterolone (Proviron)
Mibolerone (Cheque Drops)

NB: many of these products are no longer available from the original manufacturers and are now manufactured by "underground" laboratories in the United States, Mexico, and Canada, but are still widely available in certain countries, in most cases from a subsidiary of the original manufacturer (e.g. Schering, Organon).

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Gestrinone

Systematic (IUPAC) name

13-ethyl-17alpha-hydroxy-18,19 dinorpregna-4,9,11-trien-20-yn-3-one

Identifiers

CAS number rn=1" href="http://www.nlm.nih.gov/cgi/mesh/2006/MB_cgi?term=16320-04-0&rn=1"> 16320-04-0

ATC code G03**XA02**

PubChem 27812

Chemical data

Formula $C_{21}H_{24}O_2$

Mol. weight 308.4 g/mol

Pharmacokinetic data

Metabolism Hepatic

Excretion Renal, fecal

Therapeutic considerations

Pregnancy cat. X

Gestrinone is a synthetic steroid hormone that acts as an anti-progestin and also has some androgenic activity. It is marketed under the names *Dimetriose*, *Dimetrose*, and *Nemestran*, as a treatment for endometriosis. Gestrinone is available in many countries, but not in the USA. As it has anabolic effects, its use in competition has been banned by the International Olympic Committee.[1]

Method of action

Its mechanism of action consists of suppression of the release of pituitary gonadotropins. Gestrinone also interacts with the endometrium, inhibiting its growth. The inhibition is the result of gestrinone's interaction with the androgen receptor; this is also the reason for androgenic side effects. Gestrinone has been shown to interact with the estrogen receptor, the androgen receptor, and the progesterone receptor.[2]

Metabolism

The drug is well absorbed via the oral route, passed through the liver, and has a half-life of about 24 hours. It is metabolized by the liver and excreted by urine and feces.

Contraindications and side effects

The drug is contraindicated in pregnancy, during lactation, and in patients with severe cardiac, renal or hepatic insufficiency. It is also contraindicated in patients who experienced metabolic and/or vascular disorders during previous estrogen or progestogen therapy, or who are allergic to the medication. The drug is contraindicated in children.

Side effects include vaginal spotting, and, in susceptible individuals, signs of increased androgen activity such as acne, oily skin, fluid retention, weight gain, hirsutism, voice change, or hair loss.

Other uses

The drug has also been investigated for use as a prospective contraceptive agent and as a postcoital contraceptive.[3] It also has been used to shrink uterine fibroids and to reduce menorrhagia[4][5]

Its androgenic properties are more exploited in a "designer steroid", the derivative tetrahydrogestrinone. THG was banned by the Food and Drug Administration (FDA) in 2003.

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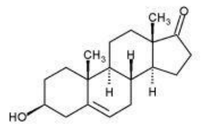
Dehydroepiandrosterone



Systematic (IUPAC) name

3ß-hydroxy-5-androsten-17-one

Identifiers

CAS number rn=1" href="http://www.nlm.nih.gov/cgi/mesh/2006/MB_cgi?term=53-43-0&rn=1"> 53-43-0

ATC code A14**AA07**

PubChem 76

Chemical data

Formula $C_{19}H_{28}O_2$

Mol. weight 288.43

Physical data

Melt. point 148.5 °C (299 °F)

Pharmacokinetic data

Metabolism Hepatic

Half life 12 hours

Excretion Urinary:?%

Therapeutic considerations

Legal status Commercially available (US)

Routes Oral

Dehydroepiandrosterone (*DHEA*), is a natural steroid hormone produced from cholesterol by the adrenal glands, the gonads, adipose tissue and the brain. DHEA is the precursor of,

androstenedione, testosterone and estrogen. It is the most abundant hormone in the human body.

Synonyms and brand names

Synonyms for Dehydroepiandrosterone are: Dehydroisoandrosterone; 3^2-Hydroxy-5-androsten-17-one; 3^2-Hydroxyandrost-5-en-17-one; Androstenol; Androstenolone; Dehydroisoandrosterone; Hydroxyandrost-5-en-17-one; Prasterone; trans-Dehydroandrosterone.

Brand names for DHEA include Prastera® and Fidelin®.

DHEAS (Dehydroepiandrosterone sulfate)

Dehydroepiandrosterone sulfate (*DHEAS*, PubChem 12594) is the sulfated version of DHEA, - this conversion is reversibly catalyzed by sulfotransferase (SULT2A1) primarily in the adrenals, the liver, and small intestines. In blood, most DHEA is found as DHEAS with levels that are about 300 times higher than free DHEA. Orally ingested DHEA is converted to its sulfate when passing through intestines and liver. While DHEA levels reach their peak in the early morning hours, DHEAS levels show no diurnal variation.

From a practical point measurement of DHEAS is preferable to DHEA as levels are more stable.

Production

DHEA is produced from cholesterol through two cytochrome P450 enzymes. Cholesterol is converted to pregnenolone by the enzyme P450 scc (side chain cleavage) and then another enzyme CYP17A1 converts pregnenolone to 17±-Hydroxypregnenolone and then to DHEA. In humans DHEA is the dominant steroid hormone and precursor of all sex steroids. Humans produce DHEA in greater quantity than any other species. Even non-human primates have not much more than 10% the relative serum level of DHEA seen in humans. The fact that rodents produce so little DHEA makes the results of experiments conducted with these laboratory animals very controversial.

DHEA production is very high during fetal life by the fetal adrenal glands, declines after birth and remains low during childhood. Production begins around 6 years of age, increasing in quantity until peaking in early adulthood, around the age of 25, and declines afterwards to approximately 10% of peak levels by age 80. It is theorized by some that this decline may be due to reduced oxygen and glucose supply to the adrenal glands as a result of age-related atherosclerosis.

Role

In a simple view DHEA can be understood as a prohormone for the sex steroids. Its DHEAS variation may be looked at as buffer and reservoir. Its production in the brain suggests that is also has a role as a neurosteroid. As most DHEA is produced by the zona

reticularis of the adrenal, it is argued that there is a role in the immune and stress response. DHEA may have more biologic roles.

As almost all DHEA is derived from the adrenal glands, blood measurements of DHEAS/DHEA are useful to detect excess adrenal activity as seen in adrenal cancer or hyperplasia, including certain forms of congenital adrenal hyperplasia. Women with polycystic ovary syndrome tend to have normal or mildly elevated levels of DHEAS.

Effects

Studies have shown that DHEA is useful in patients with systemic lupus erythematosus. An application of the evidence was reviewed by the FDA in 2001 and is available online.[1] This review also shows that cholesterol and other serum lipids decrease with the use of DHEA.

Supplementation with DHEA has been shown to decrease insulin resistance.[2]

Long term supplementation has been shown to improve mood and relieve depression.[3]

Disputed effects

The significance of the hormone in health and disease is not fully established. It is postulated that DHEA supplements are beneficial in alleviating:

- cardiovascular disease
diabetes
hypercholesterolemia
obesity
multiple sclerosis

- Parkinson's disease

- Alzheimer's disease
disorders of the immune system
depression
osteoporosis
decreased libido
decreased orgasmic intensity

It is also commercially advertised that DHEA:

- helps decrease insulin resistance
- improves fat metabolism
- increases immune system function
- has anti-aging properties
- increases lean muscle mass

7-Keto™ DHEA, a recently identified natural metabolite of dehydroepiandrosterone (DHEA) is claimed to be both more effective and safer than DHEA because it does not convert itself into testosterone or estrogens in the body.

DHEA and DHEAS are readily available in the United States, but not in many other countries.

Precautions

Some assert that DHEA should not be supplemented outside specialist centres under careful observation of experts in the field of endocrinology.

Side effects may include:

- Palpitations and other arrhythmias
extensive growth of body hair, or hirsutism
Hair loss, especially male pattern baldness
acne

Contraindication

As DHEAS and DHEA are converted to sex steroids, their use is contraindicated in patients with any cancer that is estrogen or testosterone dependent.

Increasing endogenous production

Regular exercise is known to increase DHEA production in the body.[4][5][6] Caloric restriction has also been shown to increase DHEA in primates.[7]

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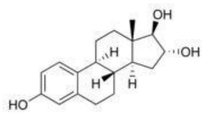
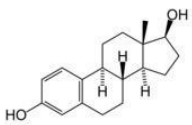
Further reading

- Nutrition through the Life Cycle, Judith E. Brown, ISBN 0-534-58986-3

Estrogens


Estriol. Note two hydroxyl (-OH) groups attached to the D ring (rightmost ring).


Estradiol. Note one hydroxyl group attached to the D ring. The 'di' refers both to this hydroxyl and the one on the A ring (leftmost).

Estrogens (also *oestrogens*) are a group of steroid compounds, named for their importance in the oestrus cycle, and functioning as the primary female sex hormone. While estrogens are present in both men and women, they are usually present at significantly higher levels in women of reproductive age. They promote the development of female secondary sex characteristics, such as breasts, and are also involved in the thickening of the endometrium and other aspects of regulating the menstrual cycle.

Explanation

The three major naturally occurring estrogens in women are estradiol, estriol and estrone. From menarche to menopause the primary estrogen is estradiol 17beta. In the body these are all produced from androgens through enzyme action. Estradiol is produced from testosterone and estrone from androstenedione. Estrone is weaker than estradiol, and in post-menopausal women more estrone is present than estradiol.

Estrogens are used as part of some oral contraceptives and also in estrogen replacement therapy of post-menopausal women.

Like all steroid hormones, estrogens readily diffuse across the cell membrane. Inside the cell, they interact with estrogen receptors.[1] A range of synthetic and natural substances have been identified that also possess estrogenic activity.[2] Synthetic substances of this kind are known as xenoestrogens, while natural plant products with estrogenic activity are called phytoestrogens.

Estrogen production

Estrogen is produced primarily by developing follicles in the ovaries, the corpus luteum and the placenta. Follicle stimulating hormone (FSH) and luteinizing hormone (LH) stimulate the production of estrogen in the ovaries. Some estrogens are also produced in smaller amounts by other tissues such as the liver, adrenal glands and the breasts. These secondary sources of estrogen are especially important in post-menopausal women.

Synthesis of estrogens starts in theca interna cells in the ovary, by the synthesis of androstenedione from cholesterol. Androstenedione is a substance of moderate androgenic activity. This compound crosses the basal membrane into the surrounding granulosa cells, where it is converted to estrone or estradiol, either immediately or through testosterone.

The conversion of testosterone to estradiol, and of androstenedione to estrone, is catalyzed by the enzyme aromatase.

Estradiol levels vary through the menstrual cycle, with levels highest just before ovulation.

Functions of estrogens

- structural
  - promote formation of female secondary sex characteristics
  - stimulate endometrial growth
  - increase uterine growth
  - maintenance of vessel and skin
  - reduce bone resorption, increase bone formation
- protein synthesis
  - increase hepatic production of binding proteins
- coagulation
  - increase circulating level of factors 2,7,9,10, antithrombin III, plasminogen
  - increase platelet adhesiveness
- lipid
  - increase HDL, triglyceride, fat deposit
  - decrease LDL
- fluid balance
  - salt and water retention
- gastro-intestinal tract
  - reduce bowel motility
  - increase cholesterol in bile

Studies have found better correlation between sexual desire and androgen levels than for estrogen levels.[3]

In studies involving mice and rats, it was found that lung function may be improved by estrogen. In one study involving 16 animals, female mice that had their ovaries removed to deprive them of estrogen lost 45 percent of their working alveoli from their lungs. Upon receiving estrogen, the mice recovered full lung function. Two proteins that are activated by estrogen play distinct roles in breathing. One protein builds new alveoli, the other stimulates the alveoli to expel carbon dioxide. Loss of estrogen hampered both functions in the test mice.[4]

Medical applications

Since estrogen circulating in the blood can feedback to reduce circulating levels of FSH and LH, most oral contraceptives contain a synthetic estrogen, along with a synthetic progestin.

In hormone replacement therapy, estrogen and other hormones are given to postmenopausal women in order to prevent osteoporosis as well as treat the symptoms of

menopause such as hot flashes, vaginal dryness, urinary stress incontinence, chilly sensations, dizziness, fatigue, irritability, and sweating. Fractures of the spine, wrist, and hips decrease by 50-70% and spinal bone density increases by ~5% in those women treated with estrogen within 3 years of the onset of menopause and for 5-10 years thereafter. Standard therapy is 0.625 mg/day of conjugated estrogens (such as is in Premarin), but the dose can range from 0.3 mg/day to 1.25 mg/day. Estrogen replacement therapy also has favorable effects on serum cholesterol levels and is claimed to dramatically reduce the incidence of cardiovascular disease. There are, however, risks associated with estrogen therapy. Among the older postmenopausal women studied as part of the Women's Health Initiative (WHI), an orally-administered estrogen supplement has been associated with an increased risk of dangerous blood clotting. The WHI studies used one type of estrogen supplement, a high oral dose of conjugated equine estrogens (Premarin alone and with Provera as Prempro)[1]. Research is underway to determine if risks of estrogen supplement use are the same for all estrogen supplement types. In particular, topically-applied estrogen may have a different spectrum of side-effects than does estrogen administered by the oral route[2].

Estrogen is also used in the therapy of vaginal atrophy, hypoestrogenism (as a result of hypogonadism, castration, or primary ovarian failure), amenorrhea, dysmenorrhea, and oligomenorrhea. Estrogens can also be used to suppress lactation after child birth.

Health risks and warning labels

The labeling of estrogen-only products includes a boxed warning that unopposed estrogen (without progestogen) therapy increases the risk of endometrial cancer.

Based on a review of data from the WHI, on January 8, 2003 the FDA changed the labeling of all estrogen and estrogen with progestin products for use by postmenopausal women to include a new boxed warning about cardiovascular and other risks. The estrogen-alone substudy of the WHI reported an increased risk of stroke and deep vein thrombosis (DVT) in postmenopausal women 50 years of age or older and an increased risk of dementia in postmenopausal women 65 years of age or older using 0.625 mg of Premarin conjugated equine estrogens (CEE). The estrogen-plus-progestin substudy of the WHI reported an increased risk of myocardial infarction, stroke, invasive breast cancer, pulmonary emboli and DVT in postmenopausal women 50 years of age or older and an increased risk of dementia in postmenopausal women 65 years of age or older using 0.625 mg of CEE with 2.5 mg of the progestin medroxyprogesterone acetate (MPA).[5][6][7]

Estrogens in cosmetics

Some hair shampoos on the market include estrogens and placental extracts; others contain phytoestrogens. There are case reports of young children developing breasts after exposure to these shampoos. The FDA is aware of these reports but does not consider them of concern to consumers.[8] These products are especially popular with African-American consumers.[9][10]

On September 9, 1993, the FDA determined that all topically-applied hormone-containing drug products for OTC human use are not generally recognized as safe and

effective and are misbranded. An accompanying proposed rule deals with cosmetics, concluding that any use of natural estrogens in a cosmetic product makes the product an unapproved new drug and that any cosmetic using the term "hormone" in the text of its labeling or in its ingredient statement makes an implied drug claim, subjecting such a product to regulatory action.[11]

In addition to being considered misbranded drugs, products claiming to contain placental extract may also be deemed to be misbranded cosmetics if the extract has been prepared from placentas from which the hormones and other biologically active substances have been removed and the extracted substance consists principally of protein. The FDA recommends that this substance be identified by a name other than "placental extract" and describing its composition more accurately because consumers associate the name "placental extract" with a therapeutic use of some biological activity.[11]

The History of Estrogen

The existence and effects of estrogen were established from 1923 to 1938 in which the formulation was led by a group of scientists instead of pharmaceutical companies. Thereafter, the market for hormonal drug research opened up.

The “first orally effective estrogen”, Emmenin, derived from the late-pregnancy urine of Canadian women was introduced in 1930 by Collip and Ayerst Laboratories. However, scientists continued to search for new sources of estrogen because of the concerns associated with the practicality of introducing the drug into the market. At the same time, a German pharmaceutical drug company, Schering, formulated a similar product as Emmenin that was introduced to German women to treat menopausal symptoms.

In 1938, British scientists obtained a patent on a newly formulated nonsteroidal estrogen, Diethylstilbestrol (DES), that was cheaper and more powerful than the previously manufactured estrogens. Soon after, concerns over the side effects of DES were raised in scientific journals while the drug manufacturers came together to lobby for governmental approval of DES. It was only until 1941 when estrogen therapy was finally approved by the Food and Drug Administration (FDA) for the treatment of menopausal symptoms. [12]

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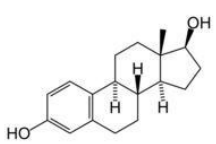
See also

- Progesterone
- Estradiol

Estradiol



Systematic (IUPAC) name

*(8S,9S,13S,14S,17S)-13-methyl-
6,7,8,9,11,12,14,15,16,17-decahydro
cyclopenta[a]phenanthrene-3,17-diol*

Identifiers

CAS number 50-28-2

ATC code G03**CA03**

PubChem 5757

Chemical data

Formula $C_{18}H_{24}O_2$

Mol. weight 272.39

Pharmacokinetic data

Bioavailability 97-99% is bound

Metabolism Liver

Half life ~ 13 hours

Excretion Urine

Therapeutic considerations

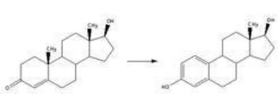
Pregnancy cat. X (USA)

Legal status S4 (Au), POM (UK), -only (U.S.)

Routes Oral, transdermal

Estradiol (17^2-estradiol) (also *oestradiol*) is a sex hormone. Labelled the "female" hormone but also present in males it represents the major estrogen in humans. Estradiol has not only a critical impact on reproductive and sexual functioning, but also affects other organs including bone structure.

Synthesis


Conversion of testosterone to estradiol

Estradiol, like other sex steroids, is derived from cholesterol. After side chain cleavage and utilizing the delta-5 pathway or the delta-4 pathway androstenedione is the key intermediary. Androstenedione is either converted to testosterone which in turn undergoes aromatization to estradiol, or, alternatively, androstenedione is aromatized to estrone which is converted to estradiol.

Production

During the reproductive years most estradiol in women is produced by the granulosa cells of the ovaries by aromatization of testosterone from the theca cells, or conversion of estrone to estradiol. Smaller amounts of estradiol are also produced by the adrenal cortex. In men, the testes produce estradiol.

Estradiol is not only produced in the gonads. In both sexes precursor hormones, specifically testosterone, are converted by aromatization to estradiol. Particularly fat cells are active to convert precursors to estradiol, and will continue to do so even after the menopause. Estradiol is thus produced also in the brain and in the wall of arterial blood vessels.

Mechanism of action

Estradiol enters cells freely and interacts with a cytoplasmic target cell receptor. When the estrogen receptor has bound its ligand it can enter the nucleus of the target cell, and regulate gene transcription which leads to formation of messenger RNA. The mRNA interacts with ribosomes to produce specific proteins that express the effect of estradiol upon the target cell.

Estradiol binds well to both estrogen receptors, ER± and ER^2, in contrast to certain other estrogens, notably medications that preferentially act on one of these receptors. These medications are called selective estrogen receptor modulators, or SERMs.

Recently there has been speculation about a membrane estrogen receptor, ERX.

Metabolism

In plasma estradiol is largely bound to sex hormone binding globulin, also to albumin, - only a fraction is free and biologically active. Deactivation includes conversion to less active estrogens such as estrone and estriol. Estriol is the major urinary metabolite. Estradiol is conjugated in the liver by sulfate and glucuronide formation and as such excreted via the kidneys. Some of the watersoluble conjugates are excreted via the bile duct, and partly reabsorbed after hydrolysis from the intestinal tract. This enterohepatic circulation contributes to maintaining estradiol levels.

Measurement

Serum estradiol measurement in women reflect primarily the activity of the ovaries. As such they are useful the detect baseline estrogen in women with amenorrhea or menstrual dysfunction and to detect state of hypoestrogenicity and menopause. Furthermore estrogen

monitoring during fertility therapy assesses follicular growth and useful to monitor the treatment. Estrogen-producing tumors will demonstrate persistent high levels of estradiol and other estrogens. In precocious puberty estradiol levels are inappropriately increased.

In the normal menstrual cycle estradiol levels measure typically <50 ng/ml at menstruation, rise with follicular development, drop briefly at ovulation, and rise again during the luteal phase for a second peak. At the end of the luteal phase estradiol levels drop to their menstrual levels unless there is a pregnancy.

During pregnancy estrogen levels including estradiol rise steadily towards term. The source of these estrogens is the placenta that aromatizes prehormones produced in the fetal adrenal gland.

Effects

Female reproduction

In the female, estradiol acts as a growth hormone for tissue of the reproductive organs, supporting the lining of the vagina, the cervical glands, the endometrium and the lining of the fallopian tubes. It enhances growth of the myometrium. Estradiol appears necessary to maintain oocytes in the ovary. During the menstrual cycle, estradiol that is produced by the growing follicle triggers via a positive feedback system the hypothalamic-pituitary events that lead to the luteinizing hormone surge, inducing ovulation. In the luteal phase estradiol , in conjunction with progesterone, prepares the endometrium for implantation. During pregnancy estradiol increases due to placental production. In baboons, blocking of estrogen production leads to pregnancy loss suggesting that estradiol has a role in the maintenance of pregnancy. Research is investigating the role of estrogens in the process of initiation of labor.

Sexual development

The development of secondary sex characteristics in women is driven by estrogens, specifically estradiol. These changes are initiated at the time of puberty, most enhanced during the reproductive years, and become less pronounced with declining estradiol support after the menopause. Thus, estradiol enhances breast development, and is responsible for changes in the body contour affecting bones, joints, fat deposition. Fat structure and skin composition are modified by estradiol.

Male reproduction

The effect of estradiol (and estrogens) upon male reproduction is complex. Estradiol is produced in the Leydig cell of the testes. There is evidence that estradiol is to prevent apoptosis of male germ cells.[1]

Several studies have noted that sperm counts have been declining in many parts of the world and it has been postulated that this may be related to estrogen exposure in the environment. [2] Suppression of estradiol production in a subpopulation of subfertile men may improve the semen analysis.[3]

Males with sex chromosome genetic conditions such as Klinefelters Syndrome will have a higher level of estradiol.

Bone

There is ample evidence that estradiol has a profound effect on bone. Individuals without estradiol (or other estrogens) will become tall and eunuchoid as epiphysieal closure is delayed or may not take place. Bone structure is affected resulting in early osteopenia and

osteoporosis. [4] Also, women past menopause experience an accelerated loss of bone mass due to a relative estrogen deficiency.

Liver

Estradiol has complex affects on the liver. It can lead to cholestasis. It affects the production of multiple proteins including lipoproteins, binding proteins, and proteins responsible for blood clotting.

Brain

Estrogens can be produced in the brain from steroid precursors. As an antioxidant, they have been found to have neuroprotective function.[5]

The positive and negative feedback loop of the menstrual cycle involve ovarian estradiol as the link to the hypothalamic-pituitary system to regulate gonadotropins.

Blood vessels

Estrogen affects certain blood vessels. Improvement in arterial blood flow has demonstrated in coronary arteries.[6]

Oncogene

Estrogen is considered an oncogene as its supports certain cancers, notably breast cancer and cancer of the uterine lining. In addition there are several benign gynecologic conditions that are dependent on estrogen such as endometriosis, leiomyomata uteri, and uterine bleeding.

Pregnancy

The effect of estradiol, together with estrone and estriol, in pregnancy is less clear. They may promote uterine blood flow, myometrial growth, sitmulate breast growth and at term, promote cervical softening and expression of myometrial oxytocin receptors.

Role in sexual differentiation

One of the fascinating twists to mammalian sexual differentiation is that estradiol is one of the two active metabolites of testosterone in males (the other being dihydrotestosterone). Estradiol cannot be transferred readily from the circulation into the brain. Since fetuses of both sexes are exposed to similarly high levels of maternal estradiol, it can play little role in prenatal sexual differentiation. However, testosterone enters the central nervous system more freely and significant amounts are aromatized to estradiol within the brain of most male mammals, including humans. There is now much evidence that the programming of

adult male sexual behavior in "lower mammals," (such as mounting rather than lordosis behavior), is largely dependent on estradiol produced in the central nervous system during prenatal life and early infancy from testosterone. We do not yet know whether this process plays a minimal or significant part in human sexual behaviors.

Estradiol medication

Estrogen is marketed in a number of ways to address issues of hypoestrogenism. Thus there are oral, transdermal, topical, injectable, and vaginal preparations. Furthermore, the estradiol molecule may be linked to an alkyl group at C3 position to facilitate the administration. Such modifications give rise to *estradiol acetate* (oral and vaginal applications) and to *estradiol cyprionate* (injectable).

Oral preparations are not necessarily predictably absorbed and subject to a first pass through the liver where they can be metabolized and also initiate unwanted side effects. Thus, alternative routes of administration have been developed that bypass the liver before primary target organs are hit. Transdermal and transvaginal routes are not subject to the initial liver passage.

A more profound alteration is ethinylestradiol, the most common estrogen ingredient in oral contraceptive medication.

Therapy

Hormone replacement therapy

In the event that levels of estradiol in a woman's blood are low (possibly due to menopause or oophorectomy), a hormone replacement therapy may be prescribed. Often such therapy is combined with a progestin.

Estrogen therapy may be used in fertility therapy when there is a need to develop cervical mucus or an appropriate uterine lining.

Estrogen therapy is also used to maintain female hormone levels in male-to-female transsexuals.

Blocking estrogens

Inducing a state of hypoestrogenism may be beneficial in certain situations where estrogens are contributing to unwanted effects, e.g, certain forms of breast cancer, gynecomastia, and premature closure of epiphyses. Estrogen levels can be reduced by inhibiting production using gonadotropin- releasing factor agonists (GnRH agonists) or blocking the aromatase enzyme using an aromatase inhibitor, or estrogen effects can be reduced with estrogen antagonists such as Tamoxifen. Flaxseed is known to reduce estradiol.[7]

Hormonal contraception

A synthetic form of estradiol, called ethinylestradiol is a major component of hormonal contraceptive devices. Combined oral contraceptives contain ethinylestradiol and a progestin, which both contribute to the inhibition of GnRH, LH, and FSH. The inhibition of these hormones accounts for the ability of combined oral contraceptives or birth control pills to prevent ovulation and thus prevent pregnancy. Other types of hormonal birth control contain only progestins and no ethinylestradiol.

List of estradiol medications

The following are marketed versions of estradiol:

- Oral versions: Estrace®, Activella® (also contains a progestin), estradiol acetate, Progynova®, estrofem®
- Transdermal preparation: Alora®, Climara®, Vivelle®, Menostar®, Estraderm TTS®
- Ointments: Estrasorb Topical®, Estrogel®
- Injection: Estradiol cyprionate: Lunelle® monthly injection, Estradiol valerate
- Vaginal ointment: Estrace Vaginal Cream®, Premarin Cream®
- Vaginal ring: Estring® (estradiol acetate)

Estradiol is also part of conjugated estrogen preparations, including Premarin®.

Contraindications

Estradiol should not be given to women who are pregnant or are breastfeeding, women with unexplained uterine bleeding, certain forms of cancer, or prone to blood clotting disorders. The medication is to be kept away from children. Detailed prescription information is available [8]

Side effects

Side effects of estradiol therapy may include uterine bleeding, breast tenderness, nausea and vomiting, chloasma, cholestasis, and migraine headaches.

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See also

- androgen

Progestagens

Progestagens (also spelled progestogens or gestagens) are hormones which produce effects similar to Progesterone, the only natural progestagen. All other progestogens are synthetic and are often referred to as progestins.

All progestagens have antiestrogenic (counteracting the effects of estrogens on the body) and antigonadotropic (inhibiting the production of sex steroids by gonads) properties.

Progestogens differ in their potency (affinity for progesterone receptors) and side effects. Such side effects may be androgenic (medroxyprogesterone and most C19 progestagens), antiandrogenic (cyproterone acetate), estrogenic, glucocorticoid (some C21 progestogens) or antimineralocorticoid (progesterone).

There is a difference between natural Progesterone and all other synthetic progestagens. Because natural progesterone cannot be patented drug companies have slightly altered the natural progesterone or attached various side groups to the the basic natural progesterone molecule in order to allow them to patent their version.

Numerous studies on HRT were completed prior to the Women's Health Initiative (see external links) and some demonstrated that estrogens plus progestagens, while reducing the risk of endometrial cancer, actually increased the incidence of breast cancers.

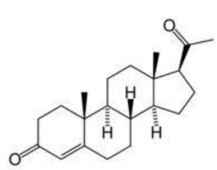
There is substantial controversy regarding the safety and effectiveness of artificial intake of hormones. While the synthetic versions of progesterone that are marketed by drug

companies have all been tested over many years by the FDA and other world-wide government bodies and are acceptably safe, recent events with drugs such as Bextra, Celebrex and Vioxx have shown that some drugs may need to be withdrawn after the FDA has become aware of doubts about their safety. This has not been the case with synthetic progestagens, which billions of women have taken for many decades in various forms. Some interested parties have threatened legal action against those individuals who claim otherwise.

Uses

- Birth control
    - Most progestogens are used for their antiestrogenic properties in oral contraceptives to avoid overstimulation of the endometrium which could lead to endometriosis and cancer.
    - Medroxyprogesterone acetate (brand name Depo Provera) is used by depot injection.
    - Etonogestrol is released by subcutaneous implants (Implanon®). Similar products (Norplant® and Jadelle® contain levonogestrol.
- Antiandrogen
    - E.g. Cyproterone.

Progesterone



Systematic (IUPAC) name

pregn-4-ene-3,20-dione

Identifiers

CAS number rn=1" href="http://www.nlm.nih.gov/cgi/mesh/2006/MB_cgi?term=57-83-0&rn=1"> 57-83-0

ATC code G03**DA04**

PubChem 5994

DrugBank APRD00700

Chemical data

Formula $C_{21}H_{30}O_2$

Mol. weight 314.47

Synonyms 4-pregnene-3,20-dione

Physical data

Melt. point 126 °C (259 °F)

Spec. rot [±]***D***

Pharmacokinetic data

Bioavailability prolonged absorption, half-life approx 25-50 hours

Protein binding 96%-99%

Metabolism hepatic to pregnanediols and pregnanolones

Half life 34.8-55.13 hours

Excretion renal

Therapeutic considerations

Pregnancy cat. B (USA)

Routes oral, implant

Progesterone is a C-21 steroid hormone involved in the female menstrual cycle, pregnancy (supports gestation) and embryogenesis of humans and other species. Progesterone belongs to a class of hormones called progestogens, and is the major naturally occurring human progestogen.

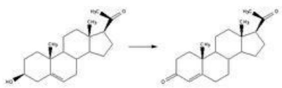
Progesterone should not be confused with progestins, which are synthetically produced progestogens.

Chemistry

Like other steroids, progesterone consists of four interconnected cyclic hydrocarbons. Progesterone contains ketone and oxygenated functional groups, as well as two methyl branches. Like all steroid hormones, it is hydrophobic. This is mostly due to its lack of very polar functional groups.

Synthesis

Progesterone, like all other steroid hormones, is synthesized from pregnenolone, a derivative of cholesterol. This conversion takes place in two steps. The 3-hydroxyl group is converted to a keto group and the double bond is moved to C-4, from C-5.



Conversion of Pregnenolone to Progesterone

Progesterone is the precursor of the mineralocorticoid aldosterone, and after conversion to 17-hydroxyprogesterone (another natural progestogen) of cortisol and androstenedione. Androstenedione can be converted to testosterone, estrone and estradiol.

Sources

Progesterone is produced in the adrenal glands, the gonads (specifically after ovulation in the corpus luteum), the brain, and, during pregnancy, in the placenta. In humans, increasing amounts of progesterone are produced during pregnancy, initially the source is the corpus luteum that has been "rescued" by the presence of human chorionic gonadotropins (hCG) from the conceptus, but after the 8th week production of progesterone shifts over to the placenta. The placenta utilizes maternal cholesterol as the initial substrate, and most of the produced progesterone enters the maternal circulation, but some is picked up by the fetal circulation and is used as substrate for fetal corticosteroids. At term the placenta produces about 250 mg progesterone per day.

Levels

In women, progesterone levels are relatively low during the preovulatory phase of themenstrual cycle, rise after ovulation, and are elevated during the luteal phase. In women progesterone levels tend to be < 2 ng/ml prior to ovulation, and > 5 ng/ml after ovulation. If pregnancy occurs, progesterone levels are maintained at luteal levels initially. With the onset of the luteal-placental shift in progesterone support of the pregnancy levels start to rise further and may reach 100-200 ng/ml at term. Whether a decrease in progesterone levels is critical for the initiation of labor has been argued and may be species-specific. After delivery of the placenta and during lactation, progesterone levels are very low.

Progesterone levels are relatively low in children and postmenopausal women. Adult males have levels similar to those in women during the follicular phase of the menstrual cycle.

Effects

Progesterone exerts its action primarily through the intracellular progesterone receptor though a distinct, membrane bound progesterone receptor has recently been discovered. It has a number of physiological effects, often regulatory, not least of the effects of estrogen. Estrogen often induces a multiplication of progesterone receptors.

Reproduction

Progesterone converts the endometrium to its secretory stage to prepare the uterus for implantation. At the same time progesterone affects the vaginal epithelium and cervical mucus. If pregnancy does not occur, progesterone levels will decrease, leading, in the human, to menstruation. Normal menstrual bleeding is progesterone withdrawal bleeding.

During implantation and gestation, progesterone appears to decrease the maternal immune response to allow for the acceptance of the pregnancy. Progesterone decreases contractility of the uterine smooth muscle. The fetus metabolizes placental progesterone in the production of adrenal mineralo- and glucosteroids. A drop in progesterone levels is possibly one step that facilitates the onset of labor. In addition progesterone inhibits lactation during pregnancy. The fall in progesterone levels following delivery is one of the triggers for milk production .

Neurosteroid

Progesterone, like pregnenolone and dehydroepiandrosterone, belongs to the group of neurosteroids that are found in high concentrations in certain areas in the brain and are synthesized there. Neurosteroids affect synaptic functioning, are neuroprotective, and affect myelinization.[1] They are investigated for their potential to improve memory and cognitive ability. Progesterone as a neuroprotectant affects regulation of apoptotic genes. Its effect as a neurosteroid works predominantly through the GSK-3 beta pathway, as an inhibitor. Other GSK-3 beta inhibitors include bipolar mood stabilizers, lithium and valproic acid. It also raises epidermal growth factor-1 levels, a factor often used to induce proliferation, and used to sustain cultures of stem cells.

Other systems

Progesterone has multiple effects outside of the reproductive system. Progesterone is thermogenic, raising the core temperature. It reduces spasm and relaxes smooth muscle. Bronchi are widened and mucus regulated. Progesterone receptors are widely present in submucosal tissue. Progesterone acts as an antiinflammatory agent and regulates the immune response. Gall-bladder activity is reduced. Other effects include normalizing blood clotting and vascular tone, zinc and copper levels, cell oxygen levels, and use of fat stores for energy. Progesterone also assists in thyroid function, in bone building by osteoblasts, in bone, teeth, gums, joint, tendon, ligament and skin resilience and in some cases healing by regulating various types of collagen, and in nerve function and healing by regulating myelin. Progesterone appears to prevent endometrial cancer (involving the uterine lining) by regulating the effects of estrogen.

Medical Applications

Progesterone is poorly absorbed by oral ingestion unless micronised and in oil, or with fatty foods; it does not dissolve in water. Products such as Prometrium, Utrogestan and

Microgest are therefore capsules containing micronised progesterone in oil - in all three mentioned that is peanut oil, which may cause serious allergic reactions in some people, but compounding pharmacies, which have the facilities and licenses to make their own products, can use alternatives. Vaginal and rectal application is also effective, with products such as Cyclogest, which is progesterone in cocoa butter in the form of pessaries. Progesterone can be given by injection, but because it has a short half-life they need to be daily. Implants, for a longer period, are also available. Marketing of progesterone phamaceutical products, country to country, varies considerably, with many countries having no oral progesterone products marketed, but they can usually be specially imported by pharmacies through international wholesalers.

"Natural progesterone" products derived from yams, do not require a prescription. Wild yams contain a plant steroid called diosgenin, which the human body cannot metabolize into progesterone. Diogenin can only be chemically processed into progesterone in labs.

Progesterone is used to control anovulatory bleeding. It is also used to prepare uterine lining in infertility therapy and to support early pregnancy. Patients with recurrent pregnancy loss due to inadequate progesterone production may receive progesterone.

Progesterone is being investigated as potentially beneficial in Multiple Sclerosis, since the characteristic deterioration of the Myelin insulation of nerves halts during pregnancy, when progesterone levels are raised, but commences again when the levels drop.

Since most progesterone in males is produced in the process of testicular production of testosterone, and most in females by the ovaries, the shutting down (whether by natural or chemical means), or removal, of those inevitably causes a considerable reduction in progesterone levels. Previous concentration upon the role of Progestagen in female reproduction, when progesterone was simply considered a "female hormone" obscured the significance of progesterone elsewhere in both sexes.

The tendency for progesterone to have a regulatory effect, and the presence of progesterone receptors in many types of body tissue, and the pattern of deterioration (or tumour formation) in many of those increasing in later years when progesterone levels have dropped, is prompting widespread research into the potential value of maintaining progesterone levels in both males and females.

Progesterone is used in hormone therapy for transsexual women, and some Intersex women - especially when synthetic progestins have been ineffective or caused side-effects - since normal breast tissue cannot develop except in the presence of both progestogen and estrogen. Mammary glandular tissue is otherwise fibrotic, the breast shape conical and the areola immature, Progesterone can correct those even after years of inadequate hormonal treatment. Research usually cited against such value was conducted using Provera, a synthetic progestin. Progesterone also has a role in skin elasticity and bone strength, in respiration, in nerve tissue and in female sexuality, and the presence of progesterone receptors in certain muscle and fat tissue may hint at a role in sexually-dimorphic proportions of those.

These roles of progesterone may not be fulfilled by synthetic progestins which were designed solely to mimic progesterone's uterine effects.

Progesterone receptor antagonists, or selective progesterone receptor modulators (SPRM)s, such as RU-486 (Mifepristone), can be used to prevent conception or induce medical abortions.

Oral birth control pills do not contain progesterone but a progestin.

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Hypolipidemic agents

Hypolipidemic agents, or *antihyperlipidemic agents*, are a diverse group of pharmaceuticals that are used in the treatment of hyperlipidemias. They are called *lipid-lowering drugs* (LLD) or agents.

Classes of hypolipidemic drugs

There are several classes of hypolipidemic drugs. They may differ in both their impact on the cholesterol profile and adverse effects. For example, some may lower the "bad cholesterol" low density lipoprotein (LDL) more so than others, while others may preferentially increase high density lipoprotein (HDL), "the good cholesterol". Clinically, the choice of an agent will depend on the patient's cholesterol profile, cardiovascular risk, and the liver and kidney functions of the patient, evaluated against the balancing of risks and benefits of the medications. In the United States, this is guided by the evidence-based guideline from the National Cholesterol Education Program (NCEP) Adult Treatment Panel III (ATPIII).

- statins are particularly well-suited for lowering LDL, the cholesterol with the strongest links to cardiovascular diseases. In studies using standard doses, statins have been found to lower LDL-C by 18% to 55%, depending on the specific statin being used. There is a risk of severe muscle damage (myopathy & rhabdomyolysis) with statins.
- fibrates are indicated for hypertriglyceridemia. Fibrates typically lower triglycerides by 20% to 50%. Level of the good cholesterol HDL is also increased. Fibrates may decrease LDL, though generally to a lesser degree than statins. Similar to statins, there is a risk of severe muscle damage (myopathy & rhabdomyolysis) with fibrates.
- nicotinic acid, like fibrates, is also well-suited for lowering triglycerides by 20-50%. It may also lower LDL by 5-25% and increase HDL by 15-35%. Nicotinic acid may cause hyperglycemia, and may also cause liver damage.
- bile acid sequestrants (resins) are particularly effective for lowering LDL-C by sequestering the cholesterol-containing bile acids released into the gut and preventing their reabsorption from the gut. It decreases LDL by 15-30% and raises HDL by 3-5%. It has little effect on triglycerides. Bile acid sequestrants may cause gastrointestinal problems, and may also reduce the absorption of other drugs and vitamins from the gut.
- ezetimibe (Zetia) is a selective inhibitor of dietary cholesterol absorption.
- phytosterols may be found naturally in plants. Similar to ezetimibe, phytosterols reduce the absorption of cholesterol in the gut. Hence, they are most effective when consumed with meals. However, the precise mechanism of action of phytosterols differs from ezetimibe.

Investigational classes of hypolipidemic agents:

- CETP Inhibitors (cholesteryl ester transfer protein inhibitors) are still under development. It is expected that these drugs will mainly increase HDL while lowering LDL.
- squalene synthase inhibitor

Fibrates

In pharmacology, the *fibrates* are a class of amphipathic carboxylic acids. They are used for a range of metabolic disorders, mainly hypercholesterolemia (high cholesterol), and are therefore hypolipidemic agents.

Members

Fibrates prescribed commonly are:

- Bezafibrate (e.g. Bezalip®)

Ciprofibrate (e.g. Modalim®)
Clofibrate (largely obsolete due to side-effect profile, e.g. gallstones)
Gemfibrozil (e.g. Lopid®)
Fenofibrate (e.g. TriCor®)

Indications

Fibrates are used as accessory therapy in many forms of hypercholesterolemia, usually in combination with statins. Trials do support its use as monotherapy.

Although less effective in lowering LDL, fibrates improve HDL and triglyceride levels, and seem to improve insulin resistance when the dyslipidemia is associated with other features of Syndrome X (hypertension and diabetes mellitus type 2).

Side effects

Most fibrates can cause mild stomach upset and myopathy (muscle pain with CPK elevations).

In combination with statin drugs, fibrates cause an increased risk of rhabdomyolysis (idiosyncratic destruction of muscle tissue, leading to renal failure). A powerful statin drug, cerivastatin (Lipobay®), was withdrawn because of this complication. The less lipophilic statins are less prone to cause this reaction, and are probably safer when combined with fibrates.

Pharmacology

Although used clinically since the early 1970s, the mechanism of action of fibrates remained unelucidated until, in the 1990s, it was discovered that fibrates activate PPAR (peroxisome proliferator-activated receptors), especially PPAR±. The PPARs are a class of

intracellular receptors that modulate carbohydrate, fat metabolism and adipose tissue differentiation.

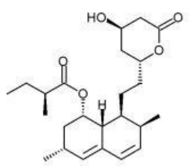
Activation of PPARs causes transcription of a number of genes on the DNA that facilitate lipid metabolism.

Fibrates are structurally and pharmacologically related to the thiazolidinediones, a novel class of anti-diabetic drugs that also act on PPARs (more specifically PPAR[3])

See also

- statin
- thiazolidinedione

Statins



Lovastatin, the first statin to be marketed

The *statins* (or *HMG-CoA reductase inhibitors*) form a class of hypolipidemic agents, used as pharmaceuticals to lower cholesterol levels in people with or at risk for cardiovascular disease. They work by inhibiting the enzyme HMG-CoA reductase, the enzyme that determines the speed of cholesterol synthesis. Inhibition of this enzyme in the liver stimulates the LDL-receptors, which results in an increased clearance of LDL from the bloodstream and a decrease in blood cholesterol levels. The first results can be seen after one week of use and the effect is maximal after four to six weeks.

Members

The statins are divided into two groups: Fermentation-derived and Synthetic. Fermentation-derived statins appear more effective in reducing LDL, but no clear explanation has accounted for this phenomenon[1].

The statins include, in alphabetical order (brand names vary in different countries):

Statin = Brand name = Derivation

Atorvastatin = Lipitor, Torvast = Synthetic

Cerivastatin = Lipobay, Baycol. (Withdrawn from the market in 2001 due to risk of serious adverse effects) = Synthetic

Fluvastatin = Lescol = Synthetic

Lovastatin = Mevacor, Altocor = Fermentation-derived

Mevastatin = - = Naturally-occurring compound. Found in red yeast rice.

Pitavastatin = Livalo, Pitava = Synthetic

Pravastatin = Pravachol, Selektine, Lipostat = Fermentation-derived

Rosuvastatin = Crestor = Synthetic

Simvastatin = Zocor, Lipex = Fermentation-derived. (Simvastatin is a synthetic derivate of a fermentation product)

LDL-lowering potency varies between agents. Cerivastatin is the most potent, followed by (in order of decreasing potency) rosuvastatin, atorvastatin, simvastatin, lovastatin, pravastatin, and fluvastatin. The relative potency of pitavastatin has not yet been fully established.

Mode of action

Cholesterol lowering

Most circulating cholesterol is manufactured internally, typically about 1000 mg/24 hours, out of the carbohydrate metabolism, by the HMG-CoA reductase pathway. Cholesterol, both from dietary intake and secreted into the duodenum as bile from the liver, is typically absorbed at a rate of 50% by the small intestines. The typical diet in the United States and many other Western countries, is estimated as adding about 200-300 mg/day to intestinal intake; much smaller than that secreted into the intestine in the bile. Thus internal production is an important factor.

Cholesterol is not water-soluble, and is therefore carried in the blood in the form of lipoproteins, the type being determined by the apoprotein, a protein coating that acts as an emulsifier. The relative balance between these lipoproteins is determined by various factors, including genetics, diet, insulin resistance. Low density lipoprotein (LDL) and very low density lipoprotein (VLDL) carry cholesterol towards tissues, and elevated levels of these lipoproteins are associated with atheroma formation (fat-containing deposits in the arterial wall) and cardiovascular disease. High density lipoprotein, in contrast, carries cholesterol back to the liver and is associated with protection against cardiovascular disease.

Statins act by competitively inhibiting HMG-CoA reductase, the first committed enzyme of the HMG-CoA reductase pathway. By reducing intracellular cholesterol levels, they cause liver cells to upregulate expression of the LDL receptor, leading to increased clearance of low-density lipoprotein from the bloodstream.[2]

Direct evidence of the action of statin-based cholesterol lowering on atherosclerosis was presented in the ASTEROID trial, which demonstrated regression of atheroma employing intravascular ultrasound.[3]

Non-cholesterol related actions

Statins exhibit action beyond lipid-lowering activity in the prevention of atherosclerosis. Researchers believe that statins prevent cardiovascular disease via four proposed mechanisms (all subjects of a large body of biomedical research):[1]

- Improving endothelial function

Modulate inflammatory responses
Maintain plaque stability
Prevent thrombus formation

Indications and uses

Statins, the most potent cholesterol-lowering agents, lower LDL-cholesterol (so-called "bad cholesterol") by 30–50%.[citation needed] However, they have less effect than the fibrates or niacin in reducing triglycerides and raising HDL-cholesterol ("good cholesterol"). Professional guidelines generally require that the patient has tried a cholesterol-lowering diet before statin use is considered. In practice, however, a cholesterol reduction of more than 10% is unusual, and many patients do not achieve their targets through dietary approaches.

The indications for the prescription of statins have broadened over the years. Initial studies, such as the Scandinavian Simvastatin Survival Study (4S), supported the use of statins in secondary prevention for cardiovascular disease, or as primary prevention only when the risk for cardiovascular disease was significantly raised (as indicated by e.g. the Framingham risk score[4]). Indications were broadened considerably by studies such as the heart protection study (HPS), which showed preventative effects of statin use in specific risk groups, such as diabetics. The ASTEROID trial published in 2006, using only a statin at high dose, and achieving lower than usual target calculated LDL values, showed disease regression within the heart arteries using IVUS.[5]

Based on clinical trials, the National Cholesterol Education Program guidelines, and the increasing focus on aggressively lowering LDL-cholesterol, the statins continue to play an important, indeed dominant and increasing role in both the primary and secondary prevention coronary heart disease, myocardial infarction, stroke and peripheral artery disease.

Research continues into other areas where statins also appear to have a favorable effect: inflammation, dementia, neoplastic conditions and pulmonary hypertension.

Pharmacogenomics

A 2004 study showed that patients with one of two common single nucleotide polymorphisms (small genetic variations) in the HMG-CoA reductase gene were less responsive to statins[6].

Safety

Adverse effects

While some patients on statin therapy report myalgias, muscle cramps, or far less-frequent gastrointestinal or other symptoms, similar symptoms are also reported with placebo use in all the large statin safety/efficacy trials and usually resolve, either on their own or on temporarily lowering/stopping the dose. Liver enzyme derangements may also occur, typically in about 0.5%, are also seen at similar rates with placebo use and repeated enzyme testing, and generally return to normal either without discontinuance over time or after briefly discontinuing the drug. Multiple other side-effects occur rarely; typically also at similar rates with only placebo in the large statin safety/efficacy trials.

A clearer major safety concern, myositis, myopathy, rarely with rhabdomyolysis (the pathological breakdown of skeletal muscle) may lead to acute renal failure when muscle breakdown products damage the kidney. Co-Enzyme Q-10 (ubiquinone) has shown promise in reducing statin-associated myalgias (statins block production of ubiquinone in addition to cholesterol). One 2004 study found that of 10,000 patients treated for one year, 0.44 will develop this side-effect. Cerivastatin, which was withdrawn by its manufacturer for this reason in 2001, had a much higher incidence (more than 10x)[7]. All commonly used statins show somewhat similar results, however the newer statins, characterized by longer pharmacological half-lifes and more cellular specificity, have had a better ratio of efficacy to lower adverse effect rates.The risk of myopathy is lowest with pravastatin and fluvastatin probably because they are more hydrophillic and as a result have less muscle penetration.

Despite initial concerns that statins might increase the risk of cancer, various studies concluded later that statins have no influence on cancer risk (including the heart protection study and a 2006 meta-analysis[8]). Indeed, a 2005 trial showed that patients taking statins for over 5 years reduced their risk of colorectal cancer by 50%; this effect was not exhibited by fibrates. The trialists warn that the number needed to treat would approximate 5000, making statins unlikely tools for primary prevention[9].

Drug interactions

Combining any statin with a fibrate, another category of lipid-lowering drugs, increases the risks for rhabdomyolysis to almost 6.0 per 10,000 person-years[7]. Most physicians have now abandoned routine monitoring of liver enzymes and creatine kinase, although they still consider this prudent in those on high-dose statins or in those on statin/fibrate combinations, and mandatory in the case of muscle cramps or of deterioration in renal function.

Consumption of grapefruit or grapefruit juice inhibits the metabolism of statins—furanocoumarins in grapefruit juice inhibit the cytochrome P450 enzyme CYP3A4, which is involved in the metabolism of most statins and some other medications[10] (it had been thought that flavonoids were responsible). This increases the levels of the statin, increasing the risk of dose-related adverse effects (including myopathy/rhabdomyolysis). Consequently, consumption of grapefruit juice is not recommended in patients undergoing

therapy with most statins. An alternative, somewhat risky, approach is that some users take grapefruit juice to enhance the effect of lower (hence cheaper) doses of statins. This is not recommended as a result of the increased risk and potential for statin toxicity.

History

Akira Endo and Masao Kuroda of Tokyo, Japan commenced research into inhibitors of HMG-CoA reductase in 1971 (Endo 1992). This team reasoned that certain microorganisms may produce inhibitors of the enzyme to defend themselves against other organisms, as mevalonate is a precursor of many substances required by organisms for the maintenance of their cell wall (ergosterol) or cytoskeleton (isoprenoids)[11].

The first agent isolated was mevastatin (ML-236B), a molecule produced by Penicillium citrinum. The pharmaceutical company Merck & Co. showed an interest in the Japanese research in 1976, and isolated lovastatin (mevinolin, MK803), the first commercially marketed statin, from the mold Aspergillus terreus. Dr Endo was awarded the 2006 Japan Prize for his work on the development of statins.

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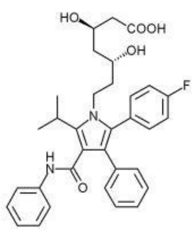
Atorvastatin (Lipitor)



Systematic (IUPAC) name

[R-(R, R*)]-2-(4-fluorophenyl)-beta, delta-dihydroxy-5- (1-methylethyl)-3-phenyl-4-[(phenylamino)carbonyl]-1H- pyrrole-1-heptanoic acid*

Identifiers

CAS number rn=1" href="http://www.nlm.nih.gov/cgi/mesh/2006/MB_cgi?term=134523-00-5&rn=1"> 134523-00-5

ATC code C10**AA05**

PubChem 60823

DrugBank APRD00055

Chemical data

Formula C***33***H***34***FN***2***O***5***

Mol. weight 558.64

Pharmacokinetic data

Bioavailability **12%**

Metabolism Liver

Half life 14 hours

Excretion Bile

Therapeutic considerations

Pregnancy cat. D(AU) X(US)

Legal status S4(AU) POM(UK) -only(US)

Routes oral

Atorvastatin (INN) (IPA: [YÈtTvYÌstætn]) is a member of the drug class known as statins, used for lowering cholesterol and thereby reducing cardiovascular disease. Atorvastatin inhibits a rate-determining enzyme located in hepatic tissue used in cholesterol synthesis, which lowers the amount of cholesterol produced. This also has the effect of lowering the total amount of LDL cholesterol.

With 2005 sales of US$12.2 billion under the brand name Lipitor, it is the largest selling drug in the world.

Pharmacology

Main article: Statin

As with other statins, atorvastatin is a competitive inhibitor of HMG-CoA reductase. Unlike most others, however, it is a completely synthetic compound. HMG-CoA reductase catalyzes the reduction of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) to mevalonate, which is the rate-limiting step in hepatic cholesterol biosynthesis. Inhibition of the enzyme decreases de novo cholesterol synthesis, increasing expression of low-density lipoprotein receptors (LDL receptors) on hepatocytes. This increases the LDL uptake by the hepatocytes, decreasing the amount of LDL in the blood.

Clinical use

Indications

Atorvastatin is indicated as an adjunct to diet for the treatment of dyslipidaemia, specifically hypercholesterolaemia. It has also been used in the treatment of combined hyperlipidemia.[1]

Available forms

Atorvastatin calcium tablets are currently marketed by Pfizer under the trade name *Lipitor*, in tablets (10, 20, 40 or 80 mg) for oral administration. Tablets are white, elliptical,

and film coated. In some countries it may also be known as: *Sortis*, *Torvast*, *Totalip*, *Tulip*, *Xarator* or *Liprimar*.

Adverse effects

Common adverse drug reactions (e1% of patients) associated with atorvastatin therapy include: myalgia, mild transient gastrointestinal symptoms, elevated hepatic transaminase concentrations, headache, insomnia, and/or dizziness.[1]

Myopathy and rhabdomyolysis occur in <0.1% of patients. Risk is increased in patients with renal impairment, serious concurrent illness; and/or concomitant use of drugs which inhibit CYP3A4.[1]

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Further reading

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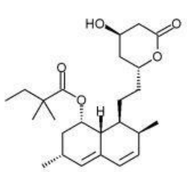
Simvastatin (Zocor)



Systematic (IUPAC) name

[(1S,3R,7R,8S,8aR)-8-[2-[(2R,4R)-4-hydroxy-6-oxo-oxan-2-yl]ethyl]-3,7-dimethyl-1,2,3,7,8,8a-hexahydronaphthalen-1-yl]2,2-dimethylbutanoate

Identifiers

CAS number 79902-63-9

ATC code C10**AA01**

PubChem 54454

DrugBank APRD00104

Chemical data

Formula $C_{25}H_{38}O_5$

Mol. weight 418.566 g/mol

Pharmacokinetic data

Bioavailability **5%**

Protein binding 95%

Metabolism Hepatic (CYP3A4)

Half life 3 hours

Excretion Renal 13%, faecal 60%

Therapeutic considerations

Pregnancy cat. $D_{(AU)}$ $X_{(US)}$

Legal status $S4_{(AU)}$ $P_{(UK)}$ -only(US)

Routes Oral

Simvastatin (INN) (IPA: [ÈsjmvYÌstætYn]) is a hypolipidemic drug belonging to the class of pharmaceuticals called "statins". It is used to control hypercholesterolemia (elevated cholesterol levels) and to prevent cardiovascular disease. Simvastatin is a synthetic derivate of a fermentation product of Aspergillus terreus.

History

The development of simvastatin was closely linked with the research and development of lovastatin. Biochemist Jesse Huff and his colleagues at Merck began researching the biosynthesis of cholesterol in the early 1950s. In 1956, mevalonic acid was isolated from a yeast extract by Karl Folkers, Carl Hoffman, and others at Merck; while Huff and his associates confirmed that mevalonic acid was an intermediate in cholesterol biosynthesis. In 1959, the HMG-CoA reductase enzyme (a major contributor of internal cholesterol production) was discovered by researchers at the Max Planck Institute. This discovery encouraged scientists worldwide to find an effective inhibitor of this enzyme.

By 1976, Akira Endo had isolated the first inhibitor (compactin ML-236B) from the fungus, Penicillium citrinium in Sankyo, Japan[1]. In 1979, Hoffman and colleagues isolated lovastatin from a strain of the fungus Aspergillus terreus. While developing and researching lovastatin, Merck scientists synthetically derived a more potent HMG-CoA reductase

inhibitor from a fermentation product of Aspergillus terreus, which was designated MK-733 (later to be named simvastatin).[2]

Uses

Simvastatin is a powerful lipid-lowering drug that can decrease low density lipoprotein (LDL) levels by up to 50%. It is used in doses of 5 mg up to 80 mg. Higher doses (160 mg) have been found to be too toxic, while giving only minimal benefit in terms of lipid lowering. There is no real effect on HDL and triglyceride levels.

From recent research it has become apparent that simvastatin and other statins inhibit the progression of atherosclerosis beyond their effects on LDL. A large number of explanations has been proposed, for example its inhibitory effect on macrophages in the atherosclerotic plaque lesions.

Rationing

Since its introduction, there has been a large debate surrounding the price for lipid-lowering treatment and its benefits on atherosclerosis. Although this has affected the other statins as well, simvastatin was the first statin drug to be used extensively in clinical practice.

A number of large epidemiological studies were conducted to discover which patients would benefit most from statin drugs; most studies involve simvastatin as the study drug. The most influential studies were the Scandinavian Simvastatin Survival Study (4S) and the Heart protection study (HPS).

It has now become apparent that patients with one or more risk factors for cardiovascular disease (such as diabetes mellitus, hypertension or a positive family history) can benefit from statins—even if they do not have substantially elevated cholesterol levels.

Simvastatin was introduced in the late 1980s, and in many countries it is now available as a generic preparation. This has led to a decrease of the price of most statin drugs, and a reappraisal of the health economics of preventive statin treatment.

In the UK, simvastatin (in a dose of 10mg) has recently become available to purchase from pharmacies without prescription.

Pharmacology

Main article: Statin

All statins act by inhibiting HMG-CoA reductase, the rate-limiting enzyme of the HMG-CoA reductase pathway, the metabolic pathway responsible for the endogenous production of cholesterol.

The drug is the form of an inactive lactone that is hydrolized after ingestion to produce the active agent. It is a white, nonhygroscopic, crystalline powder that is practically insoluble in water, and freely soluble in chloroform, methanol and ethanol.

Interactions

Grapefruit contains the flavanones naringenin and bergamottin, which inhibit the liver cytochrome P450 3A4. This in turn slows metabolization of simvastatin and a large number of other drugs. Therefore, patients taking simvastatin should restrict their intake of grapefruit and grapefruit-containing products. [3]

Marketing

Reference: Drug Discovery Today editorial, 2005.[4]

Brand names: Zocor®, Zocor Heart Pro®, marketed by the pharmaceutical company Merck & Co. and Denan (Germany), Liponorm, Sinvacor, Sivastin (Italy), Lipovas (Japan), Lodales (France), Zocord (Austria and Sweden), Zimstat, Simvahexal and Lipex (Australia) and other.

The primary US patent for Zocor expired on June 23, 2006; Ranbaxy Laboratories (at the 80-mg strength) and Teva Pharmaceutical Industries thru its Ivax Pharmaceuticals unit (at all other strengths) were given approval by the FDA to manufacture and sell simvastatin as a generic drug with 180-day exclusivity. Dr. Reddy's Laboratories also has a license from Merck & Co. to sell simvastatin as an authorized generic drug.

Ezetimibe/simvastatin is a combination product to lower lipids and marketed as Vytorin.

Sales

Prior to losing U.S. patent protection, simvastatin was Merck & Co.'s largest selling drug and second largest selling cholesterol lowering drug in the world; it recorded 4.3 billion dollars of sales in 2005.[4] Zocor had an original patent expiration date of January 2006 but was extended by the United States Federal Drug Administration (FDA) o expire on June 23, 2006. The FDA granted the patent extension after Merck & Co, Inc. submitted data from studies of the drug's positive effect on children, a move typically used by drug companies to lengthen exclusivity.[4]

Ordinarily, Merck & Co. would have expected a sharp decrease in sales after the generic versions of simvastatin entered the market; however, Merck has slashed the price of Zocor dramatically in an effort to claim sales that would have otherwise gone to the generic versions. At least two major U.S. health insurers, UnitedHealthcare and WellPoint, are now offering Zocor to their members at generic copays.[5]

In addition, since Merck & Co. itself manufactures at least some versions of Dr. Reddy's authorized generic simvastatin, and since only Dr. Reddy's can supply generic simvastatin in all available strengths (unlike Teva and Ranbaxy), Merck & Co. is also poised to profit from the Dr. Reddy's version. An 80mg, 30-count bottle of Dr. Reddy's simvastatin obtained July 6, 2006, states it is made by Merck Sharp & Dohme (Merck & Co.'s name outside the US to avoid conflicts with Merck KGaA) in the UK, just like 80mg Zocor, and has a Merck & Co. logo on the bottom; except for omitting the "80" on one side, the pills are visually identical to 80mg Zocor, including "543" on the other side which is the key part of the National Drug Code for 80mg Zocor.

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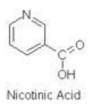
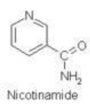
Niacin





Systematic name 3-Pyridinecarboxylic acid

Chemical formula $C_6H_5NO_2$

Molecular mass 123.11 g/mol

Melting point 236.6 °C

CAS number [59-67-6]

Niacin, also known as *nicotinic acid* or *vitamin B3*, is a water-soluble vitamin whose derivatives such as NADH, NAD, NAD+, and NADP play essential roles in energy metabolism in the living cell and DNA repair.[1] The designation vitamin B3 also includes the amide form, *nicotinamide* or *niacinamide*, whose chemical formula is C6H6N2O. Severe lack of niacin causes the deficiency disease pellagra, wherein a mild deficiency slows down the metabolism decreasing cold tolerance. The recommended daily allowance of niacin is 2-12 mg a day for children, 14 mg a day for women, 16 mg a day for men, and 18 mg a day for pregnant or breast-feeding women.[2]

Discovery

Nicotinic acid was first discovered from the oxidation of nicotine. When the properties of nicotinic acid were discovered, it was thought prudent to choose a name to dissociate it from nicotine and to avoid the idea that either smoking provided vitamins or that wholesome food contained a poison. The resulting name 'niacin' was derived from *ni*cotinic *ac*id + vitam*in*.

Vitamin B3 is also referred to as "vitamin PP", a name derived from the obsolete term "pellagra-preventing factor."

Bioavailability

The liver can synthesize niacin from the essential amino acid tryptophan (see below), but the synthesis is extremely slow; 60 mg of tryptophan are required to make one milligram of niacin. Dietary niacin deficiency tends to occur only in areas where people eat corn, the only grain low in niacin, as a staple food, and that don't use lime during maize (corn) meal/flour production. Alkali lime releases the tryptophan from the corn so that it can be absorbed in the gut, and converted to niacin.[3]

Biosynthesis

The 5-membered aromatic heterocycle of the essential amino acid, tryptophan, is cleaved and rearranged with the alpha amino group of tryptophan into the 6-membered aromatic heterocycle of niacin. By the following reaction:

Tryptophan --> Kynurenine --> 3-hydroxy kynurenine* --(B6 enzyme needed)--> Niacin

(*) from this intermediary xanthurenic acid is formed

Food Sources

Animal products:

liver, heart and kidney
chicken
fish: tuna, salmon
milk
eggs

Fruits and vegetables:

leaf vegetables
broccoli
tomatoes
carrots
dates
sweet potatoes
asparagus
avocados

Seeds:

nuts
whole grain products
legumes
saltbush seeds

Fungi:

mushrooms
brewer's yeast

Other uses

Niacin plays an important role in the production of several sex and stress-related hormones, particularly those made by the adrenal gland. It is also plays a role in removing toxic and harmful chemicals from the body.[3] There is evidence that doses of 500-1000mg can terminate a bad trip on LSD, a synthetic indole, or enhance the MDMA experience.

Niacin, when taken in large doses, increases the level of High density lipoprotein (HDL)or "good" cholesterol in blood, and is sometimes prescribed for patients with low HDL, and at high risk of heart attack.[4] Niacin (but not niacinamide) is also used in the treatment of hyperlipidemia because it reduces Very low density lipoprotein (VLDL) secretion, a precursor of Low density lipoprotein (LDL) or "bad" cholesterol, from the liver and inhibits cholesterol synthesis.[5] However, niacin is toxic to the skin and liver in overdose, and high doses of niacin should only be taken when prescribed by a knowledgeable health care provider. Studies in laboratory animals have demonstrated behavioral changes when large doses of niacin are given.[6]

Industrial use

Nicotinic acid reacts with hemoglobin and myoglobin in meat to form a brightly coloured complex, and thus has been used as a food additive, typically to improve the colour of minced (ground) meat. Niacin is licensed as a food colouring agent in some countries. i

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6. ^ Sullivan, WT (June 10, 1958). "Behavioral changes in rats and guinea pigs induced by the administration of indole 3-acetic acid and 6-aminonicotinamide". The Journal of Nutrition: 199-209. Retrieved on September 4, 2006.

Immunosuppressive agents

Immunosuppressive agents are a class of drugs which act to suppress the normal activity of the immune system. They are frequently used to prevent rejection of organs after organ transplant and also in the treatment of autoimmune disorders. Examples include azathioprine, 6-mercaptopurine, Prednisone, infliximab (Remicade), and tetracycline.

See also

- Immunosuppressive drug

Immunosuppressive drugs

Immunosuppressive drugs or *immunosuppressants* are drugs that are used in immunosuppressive therapy to inhibit or prevent activity of the immune system. Clinically they are used to:

- prevent the rejection of transplanted organs and tissues (e.g. bone marrow, heart, kidney, liver)
- treatment of autoimmune diseases or diseases that are most likely of autoimmune origin (e.g. rheumatoid arthritis, myasthenia gravis, systemic lupus erythematosus, Crohn's disease, and ulcerative colitis).
- treatment of some other non-autoimmune inflammatory diseases (eg. long term Allergic Asthma control).

These drugs are not without side effects and risks. Because the majority of them act non-selectively, the immune system loses its ability to successfully resist infections and spreading of malignant cells. There are also other side effects, like hypertension, dyslipidemia, hyperglycemia, peptic ulcers, liver and kidney injury. The immunosuppressive drugs also interact with other medicines and affect their metabolism and action.

Immunosuppressive drugs can be classified into four groups:

- glucocorticoids
- cytostatics
- antibodies
- drugs acting on immunophilins
- other drugs

Glucocorticoids

General information: Glucocorticoid.

In pharmacologic (supraphysiologic) doses, glucocorticoids are used to suppress various allergic, inflammatory, and autoimmune disorders. They are also administered as

posttransplantory immunosuppressants to prevent the acute transplant rejection and graft-versus-host disease. Nevertheless, they do not prevent an infection and also inhibit later reparative processes.

Immunosuppressive mechanism

Glucocorticoids suppress the cell-mediated immunity. They act by inhibiting genes that code for the cytokines IL-1, IL-2, IL-3, IL-4, IL-5, IL-6, IL-8 and TNF-[3], the most important of which is the IL-2. Smaller cytokine production reduces the T cell proliferation.

Glucocorticoids also suppress the humoral immunity, causing B cells to express smaller amounts of IL-2 and of IL-2 receptors. This diminishes both B cell clone expansion and antibody synthesis.

Antiinflammatory effects

Glucocorticoids influence all types of inflammatory events, no matter what their cause. They induce the lipocortin-1 (annexin-1) synthesis, which then binds to cell membranes preventing the phospholipase A2 from coming into contact with its substrate arachidonic acid. This leads to diminished eicosanoid production. The cyclooxygenase (both COX-1 and COX-2) expression is also suppressed, potentiating the effect.

Glucocorticoids also stimulate the lipocortin-1 escaping to the extracellular space, where it binds to the leukocyte membrane receptors and inhibits various inflammatory events: epithelial adhesion, emigration, chemotaxis, phagocytosis, respiratory burst and the release of various inflammatory mediators (lysosomal enzymes, cytokines, tissue plasminogen activator, chemokines etc.) from neutrophils, macrophages and mastocytes.

Cytostatics

General information: Chemotherapy

Cytostatics inhibit cell division. In immunotherapy, they are used in smaller doses than in the treatment of malignant diseases. They affect the proliferation of both T cells and B cells. Due to their highest effectiveness, purine analogs are most frequently administered.

Alkylating agents

The alkylating agents used in immunotherapy are nitrogen mustards (cyclophosphamide), nitrosoureas, platinum compounds and others. Cyclophosphamide is probably the most potent immunosuppressive compound. In small doses, it is very efficient in the therapy of systemic lupus erythematosus, autoimmune hemolytic anemias, Wegener's granulomatosis and other immune diseases. High doses cause pancytopenia and hemorrhagic cystitis.

Antimetabolites

Antimetabolites interfere with the synthesis of nucleic acids. These include:

- folic acid analogues, such as methotrexate
- purine analogues such as azathioprine and mercaptopurine
- pyrimidine analogues
- protein synthesis inhibitors.

Methotrexate

Methotrexate is a folic acid analogue. It binds dihydrofolate reductase and prevents synthesis of tetrahydrofolate. It is used in the treatment of autoimmune diseases (for example rheumatoid arthritis) and in transplantations.

Azathioprine and Mercaptopurine

Azathioprine, is the main immunosuppressive cytotoxic substance. It is extensively used to control transplant rejection reactions. It is nonenzymatically cleaved to mercaptopurine, that acts as a purine analogue and an inhibitor of DNA synthesis. Mercaptopurine itself can also be administered directly.

By preventing the clonal expansion of lymphocytes in the induction phase of the immune response, it affects both the cell and the humoral immunity. It is also efficient in the treatment of autoimmune diseases.

Cytotoxic antibiotics

Among these, dactinomycin is the most important. It is used in kidney transplantations. Other cytotoxic antibiotics are anthracyclines, mitomycin C, bleomycin, mitramycin.

Antibodies

Antibodies are used as a quick and potent immunosuppression method to prevent the acute rejection reaction.

Polyclonal antibodies

Heterologous polyclonal antibodies are obtained from the serum of animals (e.g. rabbit, horse) and injected with the patient's thymocytes or lymphocytes. The antilymphocyte (ALG) and antithymocyte antigens (ATG) are being used. They are part of the steroid-resistant acute rejection reaction and grave aplastic anemia treatment. However, they are primarily added to other immunosuppressives to diminish their dosage and toxicity. They also allow transition to cyclosporine therapy.

Polyclonal antibodies inhibit T lymphocytes and cause their lysis, which is both complement mediated cytolysis and cell-mediated opsonization followed by removal of reticuloendothelial cells from the circulation in the spleen and liver]]. In this way, polyclonal antibodies inhibit cell-mediated immune reactions, including graft rejection, delayed

hypersensitivity (i.e. tuberculin skin reaction), and the graft-versus-host disease (GVHD), but influence thymus-dependent antibody production.

Currently (March 2005) there are two preparations available to the market: Atgam (R), obtained from horse serum, and Thymoglobuline (R), obtained from rabbit serum.Polyclonal antibodies affect all lymphocytes and cause general immunosuppression possibly leading to post-transplant lymphoproliferative disorders (PTLD) or serious infections, especially by cytomegalovirus. To reduce these risks, treatment is provided in a hospital where adequate isolation from infection is available. They are usually administered for five days intravenously in the appropriate quantity. Patients stay in the hospital as long as three weeks to give the immune system time to recover to a point where there is no longer a risk of serum sickness.

Because of a high immunogenicity of polyclonal antibodies, almost all patients have an acute reaction to the treatment. It is characterized by fever, rigor episodes and even anaphylaxis. Later during the treatment, some patients develop serum sickness or immune complex glomerulonephritis. Serum sickness arises seven to fourteen days after the therapy has begun. The patient suffers from fever, joint pain and erythema that can be soothed with the use of steroids and analgesics. Urticaria (hives) can also be present. It is possible to diminish their toxicity by using highly purified serum fractions and intravenous administration in the combination with other immunosuppressants, for example calcineurin inhibitors, cytostatics and cortisteroids. The most frequent combination is to simultaneously use antibodies and cyclosporine. Patients gradually develop a strong immune response to these drugs, reducing or eliminating their effectiveness.

Monoclonal antibodies

Monoclonal antibodies are directed towards exactly defined antigens. Therefore, they cause fewer side effects. Especially significant are the IL-2 receptor (CD25) and CD3 directed antibodies. They are used to prevent the rejection of transplanted organs, but also to track changes in the lymphocyte subpopulations. It is reasonable to expect similar new drugs in the future.

T-cell receptor directed antibodies

OKT3 (R) is presently the only approved anti-CD3 antibody. It is a mouse anti-CD3 monoclonal antibody of the IgG2a type that prevents T-cell activation and proliferation by binding the T-cell receptor complex present on all differentiated T cells. As such, it is one of the most potent immunosuppressive substances and is clinically used to control the steroid and/or polyclonal antibodies resistant acute rejection episodes. For acting more specifically than polyclonal antibodies, it is also used preventively in transplantations.

Presently, the OKT3's action mechanism is not yet sufficiently understood. It is known that the molecule binds TCR/CD3, the T-cell receptor complex. During the first few administrations, this binding non-specifically activates T cells, leading to a serious syndrome 30 to 60 minutes later. It is characterized by fever, myalgia, headache and artralgia. In some cases, it progresses to a life-threatening reaction of the cardiovascular system and the central

nervous system needing a lengthy therapy. Past this period, CD3 (R) blocks the TCR - antigen binding and causes conformation change or the removal of the entire TCR3/CD3 from the T-cell surface. This lowers the number of T cells, perhaps by sensitising them for the uptake by the reticular epithelial cells. The cross-binding of CD3 molecules also activates an intracellular signal, causing the T cells' anergy or apoptosis, unless they receive another signal through a costimulatory molecule. CD3 antibodies also shift the balance from Th1 to Th2 cells.

Deciding whether to use OKT3(R) in the treatment, it is therefore necessary not only to consider its great effectiveness, but also its toxic side effects: the risk of excessive immunosuppression and the risk that the patient develops neutralizing antibodies against the drug, making it inefficacious. Although CD3(R) antibodies act more specifically than polyclonal antibodies, they lower the cell-mediated immunity significantly, predisposing the patient to opportunistic infections and malignancies.

IL-2 receptor directed antibodies

Interleukin-2 is an important immune system regulator necessary for the clone expansion and survival of activated lymphocytes T. Its effects are mediated by the trimer cell surface receptor IL-2a, consisting of the ±, ^{2} and ^{3} chains. The IL-2a (CD25, T-cell activation antigen, TAC) is expressed only by the already activated T lymphocytes. Therefore, it is of special significance to the selective immunosuppressive treatment and the research has been focused on the development of effective and safe anti-IL-2 antibodies. By the use of the recombinant gene technology, the mouse anti-Tac antibodies have been modified leading to the presentation of two himeric mouse/human anti-Tac antibodies in the year 1998: basiliximab (Simulect (R)) and daclizumab (Zenapax (R)). These drugs act by binding the IL-2a receptor's ± chain, preventing the IL-2 induced clonal expansion of activated lymphocytes and shortening their survival. They are used in the profilaxis of the acute organ rejection after the bilateral kidney transplantation, both being similarly effective and with only few side effects.

Drugs acting on immunophilins

Cyclosporin

Together with tacrolimus, cyclosporin is a calcineurin inhibitor. It has been in use since 1983 and is one of the most widely used immunosuppressive drugs. It is a fungal peptide, composed of 11 amino acids.

Cyclosporin is thought to bind to the cytosolic protein cyclophilin (an immunophilin) of immunocompetent lymphocytes, especially T-lymphocytes. This complex of ciclosporin and cyclophilin inhibits calcineurin, which under normal circumstances induces the transcription of interleukin-2. The drug also inhibits lymphokine production and interleukin release, leading to a reduced function of effector T-cells.

Cyclosporin is used in the treatment of acute rejection reactions, but has been increasingly substituted with newer immunosuppressants, as it is nephrotoxic.

Tacrolimus (Prograf(TM), FK506)

Tacrolimus is a bacterial product (Streptomyces tsukubaensis). It is a macrolide lactone and acts by inhibiting calcineurin.

The drug is used particularly in the liver and kidney transplantations, although in some clinics it is used in heart, lung and heart/lung transplants. It binds to an immunophilin, followed by the binding of the complex to calcineurin and the inhibition of its phosphatase activity. In this way, it prevents the passage of G0 into G1 phase. Tacrolimus is more potent than cyclosporin and has less pronounced side effects.

Sirolimus (Rapamune (Tm), Rapamicin)

Sirolimus is a macrolide lactone, produced by the actinomycetes Streptomyces hygroscopicus. It is used to prevent rejection reactions. Although it is a structural analogue of tacrolimus, it acts somewhat differently and has different side effects.

Contrary to cyclosporine and tacrolimus that affect the first phase of the T lymphocyte activation, sirolimus affects the second one, namely the signal transduction and their clonal proliferation. It binds to the same receptor (immunophilin) as tacrolimus, however the produced complex does not inhibit calcineurin, but another protein. Therefore, sirolimus acts synergistically with cyclosporine and, in combination with other immunosuppressants, has few side effects. Indirectly it inhibits several T lympohocyte kinases and phosphatases, preventing the transmission of signal into their activity and the transition of the cell cycle from G1 to S phase. Similarly, it prevents the B cell differentiation to the plasma cells, which lowers the quantity of IgM, IgG and IgA antibodies produced. It acts immunoregulatory.

Other drugs

Interferons

General information:Interferon.

IFN-^{2} suppresses the production of Th1 cytokines and the activation of monocytes. It is used to slow down the progression of multiple sclerosis. IFN-^{3} is able to trigger lymphocytic apoptosis.

Opioids

Prolonged use of opioids may cause immunosuppression by inhibiting the migration of leukocytes.

TNF binding proteins

A TNF-± (tumor necrosis factor alpha) binding protein is a monoclonal antibody or a circulating receptor such as infliximab (Remicade®), etanercept (Enbrel®), or adalimumab (Humira®) that binds to TNF-± and prevent it from inducing the synthesis of IL-1 and IL-6 and the adhesion of lymphocyte activating molecules. They are used in the treatment of rheumatoid arthritis, ankylosing spondylitis, Crohn's disease and psoriasis.

TNF or the effects of TNF are also suppressed by various natural compounds, including curcumin (an ingredient in turmeric) and catechins (in green tea).

These drugs may raise the risk of contracting tuberculosis or inducing a latent infection to become active. Infliximab and adalimumab have label warnings stating that patients should be evaluated for latent TB infection and treatment should be initiated prior to starting therapy with them.

Mycophenolate

Mycophenolic acid acts as a non-competitive, selective and reversible inhibitor of inosine monophosphate dehydrogenase (IMPDH), which is a key enzyme in the de novo guanosine nucleotide synthesis. In contrast to other human cell types, lymphocytes B and T are very dependent on this process.

Small biological agents

FTY720 is a new synthetic immunosuppressant, currently in phase 3 of clinical trials. It increases the expression or changes the function of certain adhesion molecules (±4/^{2}7 integrin) in lymphocytes, so they accumulate in the lymphatic tissue (lymphatic nodes) and their number in the circulation is diminished. In this respect, it differs from all other known immunosuppressants.

Inotropic agents

An *inotrope* (IPA: [ÈajnYtrop]) is an agent which increases or decreases the force or energy of muscular contractions. Negatively inotropic agents weaken the force of muscular contractions. Positively inotropic agents increase the strength of muscular contraction.

Most commonly, the term is used in reference to various drugs that affect the strength of contraction of heart muscle (myocardial contractility). Both positive and negative inotropes are used in the management of various cardiovascular conditions. The choice of agent largely depends on specific pharmacological effects of individual agents with respect to the condition.

Positive inotropic agents

Positive inotropic agents increase myocardial contractility, and are used to support cardiac function in conditions such as decompensated congestive heart failure, cardiogenic shock, septic shock, myocardial infarction, cardiomyopathy, etc.

Examples of positive inotropic agents include:

- Calcium sensitisers
  - Levosimendan

- Cardiac glycosides
  - Digoxin

- Catecholamines
  - Dopamine
  - Dobutamine
  - Dopexamine
  - Isoprenaline (isoproterenol)
  - Norepinephrine (noradrenaline)

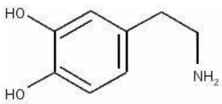
Negative inotropic agents

Negative inotropic agents decrease myocardial contractility, and are used to decrease cardiac workload in conditions such as angina. While negative inotropism may precipitate or exacerbate heart failure, certain beta blockers (e.g. carvedilol) have been shown to reduce morbidity and mortality in congestive heart failure.

- Beta blockers

- Diltiazem
- Verapamil

Dopamine



Systematic name 4-(2-aminoethyl)benzene-1,2-diol

Other names 2-(3,4-dihydroxyphenyl)ethylamine; 3,4-dihydroxyphenethylamine; 3-hydroxytyramine; DA; Intropin Revivan; Oxytyramine

Molecular formula C***8***H***11***NO***2***

SMILES C1=CC(=C(C=C1CCN)O)O

Molar mass 153.178 g/mol

Appearance white powder with distinctive smell

CAS number [51-61-6]

Properties

Solubility in water 60.0 g/100 ml (? °C), solid

Melting point 128 °C (401 K)

Hazards

R/S statement R: 36/37/38 S: 26-36

RTECS number UX1088000

Except where noted otherwise, data are given for materials in their standard state (at 25 °C, 100 kPa)

Dopamine is a chemical naturally produced in the body. In the brain, dopamine functions as a neurotransmitter, activating dopamine receptors. Dopamine is also a neurohormone released by the hypothalamus. Its main function as a hormone is to inhibit the release of prolactin from the anterior lobe of the pituitary.

Dopamine can be supplied as a medication that acts on the sympathetic nervous system, producing effects such as increased heart rate and blood pressure. However, since dopamine cannot cross the blood-brain barrier, dopamine given as a drug does not directly affect the central nervous system. To increase the amount of dopamine in the brains of patients with

diseases such as Parkinson's disease and Dopa-Responsive Dystonia, a synthetic precursor to dopamine such as L-DOPA can be given, since this will cross the blood-brain barrier.

Biochemistry

Dopamine has the chemical formula ($C_6H_3(OH)_2$-CH_2-CH_2-NH_2). Its chemical name is 4-(2-aminoethyl)benzene-1,2-diol and it is abbreviated "DA."

As a member of the catecholamine family, dopamine is a precursor to epinephrine (adrenaline) and norepinephrine (noradrenaline) in the biosynthetic pathways for these neurotransmitters. Arvid Carlsson won a share of the 2000 Nobel Prize in Physiology or Medicine for showing that dopamine is not just a precursor to these, but a neurotransmitter as well.

Dopamine is synthesized in the body (mainly by nervous tissue and adrenal glands) first by the hydration of the amino acid tyrosine to DOPA by tyrosine hydroxylase and then by the decarboxylation of DOPA by aromatic-L-amino-acid decarboxylase. In neurons, dopamine is packaged after synthesis into vesicles, which are then released in response to the presynaptic action potential. The inactivation mechanism of neurotransmission are 1) uptake via a specific transporter; 2) enzymatic breakdown; and 3) diffusion. Uptake back to the presynaptic neuron via the dopamine transporter is the major role in the inactivation of dopamine neurotransmission. The recycled dopamine will face either breakdown by an enzyme or be re-packaged into vesicles and reused.

Functions in the brain

Dopamine has many functions in the brain. Most importantly, dopamine is central to the reward system[1]. Dopamine neurons may have the role to emit a teaching signal for prioritizing and learning of reward-directed behaviour and to code reward information relative to established predictions.

Movement

Dopamine affects the basal ganglia motor loop which in turn affects the way the brain controls our movements. Shortage of dopamine, particularly the death of dopamine neurons in the nigrostriatal pathway, causes Parkinson's disease, in which a person loses the ability to execute smooth, controlled movements.

Cognition and frontal cortex

In the frontal lobes, dopamine controls the flow of information from other areas of the brain. Dopamine disorders in this region of the brain can cause a decline in neurocognitive functions, especially memory, attention and problem-solving. Reduced dopamine concentrations in the prefrontal cortex are thought to contribute to attention deficit disorder and negative schizophrenia. Conversely, anti-psychotic medications rely on their inhibition of dopamine uptake and are used in the treatment of positive symptoms in schizophrenia.

Regulating prolactin secretion

Dopamine is the primary neuroendocrine regulator of the secretion of prolactin from the anterior pituitary gland. Dopamine produced by neurons in the arcuate nucleus of the hypothalamus is secreted into the hypothalamo-hypophysial blood vessels of the median eminence, which supply the pituitary gland. The lactotrope cells that produce prolactin, in the absence of dopamine, secrete prolactin continuously; dopamine inhibits this secretion.

Motivation and pleasure

Dopamine is commonly associated with the pleasure system of the brain, providing feelings of enjoyment and reinforcement to motivate a person proactively to perform certain activities. Dopamine is released (particularly in areas such as the nucleus accumbens and striatum) by naturally rewarding experiences such as food, sex, use of certain drugs and neutral stimuli that become associated with them. This theory is often discussed in terms of drugs (such as cocaine and amphetamines), which seem to be directly or indirectly related to the increase of dopamine in these areas, and in relation to neurobiological theories of chemical addiction, arguing that these dopamine pathways are pathologically altered in addicted persons. However, cocaine and amphetamine influence separate mechanisms of action.

Cocaine is a dopamine transporter blocker that competitively inhibits dopamine uptake to increase the lifetime of dopamine and augments an overabundance of dopamine (an increase of up to 150%) within the parameters of the dopamine neurotransmitters. Like cocaine, amphetamines increase the concentration of dopamine in the synaptic gap, but by a different mechanism. Amphetamines are similar in structure to dopamine, and so can enter the terminal button of the presynaptic neuron via its dopamine transporters as well as by diffusing through the neural membrane directly. When entering inside the presynaptic neuron, amphetamines force the dopamine molecules out of their storage vesicles and expel them into the synaptic gap by making the dopamine transporters work in reverse. Dopamine's role in experiencing pleasure has been questioned by several researchers. It has been argued that dopamine is more associated with anticipatory desire and motivation (commonly referred to as "wanting") as opposed to actual consummatory pleasure (commonly referred to as "liking"). Dopamine is released when unpleasant or aversive stimuli are encountered, and so motivates towards the pleasure of avoiding or removing the unpleasant stimuli.

Recent research suggests that the firing of dopamine neurons is a motivational chemical as a result of reward-anticipation. This is based on evidence that, when a reward is perceived to be greater than expected, the firing of certain dopamine neurons increases, which correspondingly increases desire or motivation toward the reward.

Clues to dopamine's role in motivation, desire and pleasure have come from studies performed on animals. In one such study rats were depleted of dopamine by up to 99% in the nucleus accumbens and neostriatum using 6-hydroxydopamine.[1] With this large reduction in dopamine, the rats would no longer eat by their own volition. The researchers then force fed the rats food and noted whether they had the proper facial expressions

indicating whether they liked or disliked it. The researchers of this study concluded that the reduction in dopamine did not reduce the rat's consummatory pleasure, only the desire to actually eat. In another study, mutant hyperdopaminergic (increased dopamine) mice show higher "wanting" but not "liking" of sweet rewards.[2]

In humans, though, drugs that reduce dopamine activity (e.g., antipsychotics) have been shown to reduce motivation as well as cause anhedonia (the inability to experience pleasure).[3] Conversely the selective D2/D3 agonists pramipexole and ropinirole have anti-anhedonic properties as measured by the Snaith-Hamilton Pleasure Scale.[4] (The Snaith-Hamilton-Pleasure-Scale (SHAPS), introduced in English in 1995, assesses self-reported anhedonia in psychiatric patients.)

Opioid and cannabinoid transmission instead of dopamine may modulate consummatory pleasure and food palatability(liking).[5] This could explain why animals "liking" of food is independent of brain dopamine concentration. Other consummatory pleasures, however, may be more associated with dopamine. One study found that both anticipatory and consummatory measures of sexual behavior (male rats) were disrupted by DA receptor antagonists.[6] Libido can be increased by drugs that affect dopamine but not by drugs that affect opioid peptides or other neurotransmitters.

Sociability is also closely tied to dopamine neurotransmission. Low D2 receptor binding is found in people with social anxiety. Traits common to negative schizophrenia (social withdrawal, apathy, anhedonia) are thought to be related to a hypodopaminergic state in certain areas of the brain. In instances of bipolar, manic subjects can become hypersocial as well as hypersexual. This is also credited to an increase in dopamine, because mania alleviates from dopamine blocking antipsychotics.

Other theories reinforce that the crucial role of dopamine may be in desire, or anticipating pleasurable activity. Related theories [7] argue that dopamine function may be involved in the salience ('noticeableness') of perceived objects and events, with potentially important stimuli such as: 1) rewarding things or 2) dangerous or threatening things seeming more noticeable or important. This hypothesis argues that dopamine assists decision-making by influencing the priority, or level of desire, of such stimuli to the person concerned.

Pharmacological blockade of brain dopamine receptors increases rather than decreases drug-taking behavior. Since blocking dopamine decreases desire, the increase in drug taking behavior may be seen as not a chemical desire but as a deeply psychological desire to just 'feel something'.

Deficits in dopamine levels are implicated as one of several possible causes for Adult attention-deficit disorder (AADD), and some types of medications used to treat Attention-deficit hyperactivity disorder (ADHD/ADD) will help to stimulate dopaminergic systems, leading to potentially heightened sensation, for those afflicted by it and receiving treatment for it.

Links to psychosis

Disruption to the dopamine system has also been strongly linked to psychosis and schizophrenia.[8] Dopamine neurons in the mesolimbic pathway are particularly associated with these conditions. This is partly due to the discovery of a class of drugs called the

phenothiazines (which block D2 dopamine receptors) that can reduce psychotic symptoms, and partly due to the finding that drugs such as amphetamine and cocaine (which are known to greatly increase dopamine levels) can cause psychosis. Because of this, most modern antipsychotic medication is designed to block dopamine function to varying degrees.

Depression

Dopamine is a neurotransmitter that is involved in depression. Amphetamines and dopamine reuptake blockers have potent anti-depressant effects but these drugs quickly lose their benefit after they deplete dopamine levels in the brain. Antidepressants appear to primarily enhance serotonergic neurotransmission during preliminary drug administration but it takes several weeks for the antidepressant effect to be noticed. The late effect of antidepressants is thought to involve the indirect serotonergic modulation of dopaminergic neurotransmission. Blocking the D***2*** dopamine receptor is known to cause relapse in patients that have achieved remission from depression, and such blocking also counteracts the effectiveness of SSRI medication.

Therapeutic use

Levodopa is a dopamine precursor used to treat Parkinson's disease. It is typically co-administered with an inhibitor of peripheral decarboxylation (DDC, dopa decarboxylase), such as carbidopa or benserazide. Inhibitors of alternative metabolic route for dopamine by catechol-O-methyl transferase are also used. These include entacapone and tolcapone.

Dopamine is also used as an inotropic drug in patients with shock to increase cardiac output and blood pressure.

Major pathways

- Mesocortical pathway

Mesolimbic pathway
Nigrostriatal pathway
Tuberoinfundibular pathway

See also

- Amphetamine
- Antipsychotic
- Cocaine
- Dopamine reuptake inhibitors
- Methylphenidate

- Parkinson's disease

Footnotes

1. ^ Berridge K, Robinson T (1998). "What is the role of dopamine in reward: hedonic impact, reward learning, or incentive salience?". Brain Res Brain Res Rev *28* (3): 309-69. PMID 9858756.
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3. ^ Lambert M, Schimmelmann B, Karow A, Naber D (2003). "Subjective well-being and initial dysphoric reaction under antipsychotic drugs - concepts, measurement and clinical relevance.". Pharmacopsychiatry *36 Suppl 3*: S181-90. PMID 14677077.
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5. ^ **Peciña S, Berridge K (2005). "**Hedonic hot spot in nucleus accumbens shell: where do mu-opioids cause increased hedonic impact of sweetness?**". J Neurosci** *25* **(50): 11777-86.** PMID 16354936**.**
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7. ^ Schultz W (2002). "Getting formal with dopamine and reward". Neuron *36* (2): 241-263. PMID 12383780.
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Intravenous fluids

Intravenous therapy or *IV therapy* is the administration of liquid substances directly into a vein. It can be intermittent or continuous; continuous administration is called an *intravenous drip*. The word *intravenous* simply means "within a vein", but is most commonly used to refer to IV therapy. Therapies administered intravenously are often called *specialty pharmaceuticals*.

Compared with other routes of administration, the intravenous route is the fastest way to deliver fluids and medications throughout the body. Some medications, as well as blood transfusions and lethal injections, can only be given intravenously.

Intravenous access devices

Needle and syringe

The simplest form of intravenous access is a syringe with an attached hollow needle. The needle is inserted through the skin into a vein, and the contents of the syringe are injected through the needle into the bloodstream. This is most easily done with an arm vein, especially one of the metacarpal veins. Usually it is necessary to use a tourniquet first to make the vein bulge; once the needle is in place, it is common to draw back slightly on the syringe to aspirate blood, thus verifying that the needle is really in a vein; then the tourniquet is removed before injecting.

This is the most common method of intravenous drug use for euphoriants such as heroin, or in any case where a person must self-administer intravenous medication at home. It is also a convenient way to deliver life-saving medications in an emergency. However, in a controlled health-care setting, direct injection is rarely used since it only allows delivery of a single dose of medication.

Peripheral IV lines

This is the most common intravenous access method in both hospitals and paramedic services. A *peripheral IV line* consists of a short catheter (a few centimeters long) inserted through the skin into a peripheral vein. A peripheral vein is any vein that is not in the chest or abdomen. Arm and hand veins are typically used although leg and foot veins are occasionally used. On infants the scalp veins are sometimes used. Part of the catheter remains outside the skin, with a hub that can be connected to a syringe or an intravenous infusion line, or capped with a bung between treatments. The caliber of cannulae is commonly indicated in gauge, with 14 being a very large cannula (used in resuscitation settings) and 24-26 the smallest. The most common sizes are 16-gauge (midsize line used for blood donation and transfusion), 18- and 20-gauge (all-purpose line for infusions and blood draws), and 22-gauge (all-purpose pediatric line). 12 and 14-gauge peripheral lines actually deliver equivalent volumes of fluid faster than central lines, accounting for their

popularity in emergency medicine; these lines are frequently called "widebores" or "trauma lines." For illustration, please view IV Catheter pictures here.

Blood can be drawn from a peripheral IV if necessary, but only if it is in a relatively large vein and only if the IV is newly inserted. Blood draws are typically taken with specialized IV access sets known as phlebotomy kits, and once the draw is complete, the needle is removed and the site is not used again. If a patient needs frequent venous access, the veins may scar and narrow, making any future access extremely difficult or impossible; this situation is known as a "blown vein," and the person attempting to obtain the access must find a new access site proximal to the "blown" area.

Originally, a peripheral IV was simply a needle that was taped in place and connected to tubing rather than to a syringe; this system is still used for blood donation sets, as the IV access will only be needed for a few minutes and the donor may not move while the needle is in place. Today, hospitals use a safer system in which the catheter is a flexible plastic tube that originally contains a needle to allow it to pierce the skin; the needle is then removed and discarded, while the soft catheter stays in the vein. The external portion of the catheter, which is usually taped in place or secured with a self-adhesive dressing, consists of an inch or so of flexible tubing and a locking hub. Many sets contain a small amount of the anticoagulant heparin to keep the line from clotting off, and frequently are called "heparin locks" or "hep-locks."

A peripheral IV cannot be left in the vein indefinitely, because of the risk of insertion-site infection leading to phlebitis, cellulitis and bacteremia. Hospital policies usually dictate that every peripheral IV be replaced (at a different location) every three to four days to avoid this complication.

Central IV lines

Central IV lines flow through a catheter with its tip within a large vein, usually the superior vena cava or inferior vena cava, or within the right atrium of the heart. This has several advantages over a peripheral IV:

- It can deliver fluids and medications that would be overly irritating to peripheral veins because of their concentration or chemical composition. These include some chemotherapy drugs and total parenteral nutrition.
- Medications reach the heart immediately, and are quickly distributed to the rest of the body.
- There is room for multiple parallel compartments (lumens) within the catheter, so that multiple medications can be delivered at once even if they would not be chemically compatible within a single tube.
- Caregivers can measure central venous pressure and other physiological variables through the line.

Central IV lines carry higher risks of bleeding, bacteremia, and gas embolism (see Risks below).

There are several types of central IVs, depending on the route that the catheter takes from the outside of the body to the vein.

Peripherally inserted central catheter (PICC)

PICC lines are used when intravenous access is required over a prolonged period of time, as in the case of long chemotherapy regimens, extended antibiotic therapy, or total parenteral nutrition.

The PICC line is inserted into a peripheral vein, usually in the arm, and then carefully advanced upward until the catheter is in the superior vena cava or the right atrium. This is usually done by feel and estimation; an X-ray then verifies that the tip is in the right place.

A PICC may have two parallel compartments, each with its own external connector (double-lumen), or a single tube and connector (single-lumen). From the outside, a single-lumen PICC resembles a peripheral IV, except that the tubing is slightly wider.

The insertion site must be covered by a larger sterile dressing than would be required for a peripheral IV, due to the higher risk of infection if bacteria travel up the catheter. However, a PICC poses less of a systemic infection risk than other central IVs, because bacteria would have to travel up the entire length of the narrow catheter before spreading through the bloodstream.

The chief advantage of a PICC over other types of central lines is that it is easy to insert, poses a relatively low risk of bleeding, is externally unobtrusive, and can be left in place for months to years for patients who require extended treatment. The chief disadvantage is that it must travel through a relatively small peripheral vein and is therefore limited in diameter, and also somewhat vulnerable to occlusion or damage from movement or squeezing of the arm.

Central venous lines

There are several types of catheters that take a more direct route into central veins. These are collectively called central venous lines.

In the simplest type of central venous access, a catheter is inserted into a subclavian, internal jugular, or (less commonly) a femoral vein and advanced toward the heart until it reaches the superior vena cava or right atrium. Because all of these veins are larger than peripheral veins, central lines can deliver a higher volume of fluid and can have multiple lumens.

Another type of central line, called a Hickman line or Broviac catheter, is inserted into the target vein and then "tunneled" under the skin to emerge a short distance away. This reduces the risk of infection, since bacteria from the skin surface are not able to travel directly into the vein; these catheters are also made of materials that resist infection and clotting.

Implantable ports

A port (often referred to by brand names such as Port-a-Cath or MediPort) is a central venous line that does not have an external connector; instead, it has a small reservoir implanted under the skin. Medication is administered intermittently by placing a small needle through the skin into the reservoir. Ports cause less inconvenience and have a lower

risk of infection than PICCs, and are therefore commonly used for patients on long-term intermittent treatment.

Forms of intravenous therapy

Intravenous drip

An *intravenous drip* is the continuous infusion of fluids, with or without medications, through an IV access device. This may be to correct dehydration or an electrolyte imbalance, to deliver medications, or for blood transfusion.

IV fluids

There are two types of fluids that are used for intravenous drips; crystalloids and colloids. Crystalloids are aqueous solutions of mineral salts or other water-soluble molecules. Colloids contain larger insoluble molecules, such as gelatin; blood itself is a colloid.

The most commonly used crystalloid fluid is normal saline, a solution of sodium chloride at 0.9% concentration, which is close to the concentration in the blood (isotonic). Ringer's lactate or Ringer's acetate (ASERING) is another isotonic solution often used for large-volume fluid replacement. A solution of 5% dextrose in water, sometimes called D5W, is often used instead if the patient is at risk for having low blood sugar or high sodium. The choice of fluids may also depend on the chemical properties of the medications being given.

Intravenous fluids must always be sterile.

Composition of Common Crystalloid Solutions

Solution	Other Name	$[Na^+]$	$[Cl^-]$	[Glucose]
D5W	5% Dextrose	0	0	252
2/3D & 1/3S	3.3% Dextrose / 0.3% saline	51	51	168
Half-normal saline	0.45% NaCl	77	77	0
Normal saline	0.9% NaCl	154	154	0
Ringer's lactate	Lactated Ringer	130	109	0

Ringer's lactate also has 28 mmol/L lactate, 4 mmol/L K^+ and 3 mmol/L Ca^{2+}. Ringer's acetate (ASERING) also has 28 mmol/L acetate, 4 mmol/L K^+ and 3 mmol/L Ca^{2+}.

Effect of Adding One Litre

Solution	Change in ECF	Change in ICF
D5W	333 mL	667 mL
2/3D & 1/3S	556 mL	444 mL
Half-normal saline	667 mL	333 mL
Normal saline	1000 mL	0 mL
Ringer's lactate	900 mL	100 mL

Infusion equipment

A standard IV infusion set consists of a pre-filled, sterile container (glass bottle, plastic bottle or plastic bag) of fluids with an attached drip chamber which allows the fluid to flow one drop at a time, making it easy to see the flow rate (and also reducing air bubbles); a long sterile tube with a clamp to regulate or stop the flow; a connector to attach to the access device; and connectors to allow "piggybacking" of another infusion set onto the same line, e.g., adding a dose of antibiotics to a continuous fluid drip.

An infusion pump allows precise control over the flow rate and total amount delivered, but in cases where a change in the flow rate would not have serious consequences, or if pumps are not available, the drip is often left to flow simply by placing the bag above the level of the patient and using the clamp to regulate the rate; this is a gravity drip.

A rapid infuser can be used if the patient requires a high flow rate and the IV access device is of a large enough diameter to accommodate it. This is either an inflatable cuff placed around the fluid bag to force the fluid into the patient or a similar electrical device that may also heat the fluid being infused.

Intermittent infusion

Intermittent infusion is used when a patient requires medications only at certain times, and does not require additional fluid. It can use the same techniques as an intravenous drip (pump or gravity drip), but after the complete dose of medication has been given, the tubing is disconnected from the IV access device. Some medications are also given by *IV push*, meaning that a syringe is connected to the IV access device and the medication is injected directly (slowly, if it might irritate the vein or cause a too-rapid effect). Once a medicine has been injected into the fluid stream of the IV tubing there must be some means of ensuring that it gets from the tubing to the patient. Usually this is accomplished by allowing the fluid stream to flow normally and therby carry the medicine into the bloodstream; however, a

second fluid injection is sometimes used, a "flush", following the injection to push the medicine into the bloodstream more quickly.

Risks of intravenous therapy

Intravenous therapy has many risks and should therefore only be performed by trained personnel under medical supervision, using proper equipment.

Infection

Any break in the skin carries a risk of infection. Although IV insertion is a sterile procedure, skin-dwelling organisms such as Coagulase-negative Staphylococcus or Candida albicans may enter through the insertion site around the catheter, or bacteria may be accidentally introduced inside the catheter from contaminated equipment.

Infection of IV sites is usually local, causing easily visible swelling, redness, and fever. If bacteria do not remain in one area but spread through the bloodstream, the infection is called septicemia and can be rapid and life-threatening. An infected central IV poses a higher risk of septicemia, as it can deliver bacteria directly into the central circulation.

Phlebitis

Phlebitis is irritation of a vein that is not caused by infection, but from the mere presence of a foreign body (the IV catheter) or the fluids or medication being given. Symptoms are swelling, pain, and redness around the vein. It does not necessarily mean the IV device must be removed; warmth, elevation of the affected limb, or a change in the rate of flow may resolve the symptoms.

Due to frequent injections and recurring phlebitis, the peripheral veins of intravenous drug addicts, and of cancer patients undergoing chemotherapy, become hardened and difficult to access over time.

Infiltration

This occurs when the tip of the IV catheter withdraws from the vein or pokes through the vein into surrounding tissue, or when the vein's wall becomes permeable and leaks fluid (in this instance it is said that the cannula has 'tissued'). It occurs frequently with peripheral IVs, and requires replacement of the IV at a different location. The symptoms of pain and swelling are temporary and not dangerous, unless giving a highly irritating medication, such intravenous contrast or amiodarone. Additionally it can become dangerous if the person monitoring the IV site fails to recognize that an infiltration has occurred and fluid continues to drip in the tissue under the skin. It can cause a compression injury. This known as an infiltration injury.

Fluid overload

This occurs when fluids are given at a higher rate or in a larger volume than the system can absorb or excrete. Possible consequences include hypertension, heart failure, and pulmonary edema.

Electrolyte imbalance

Administering a too-dilute or too-concentrated solution can disrupt the patient's balance of sodium, potassium, magnesium, and other electrolytes. Hospital patients usually receive blood tests to monitor these levels.

Embolism

A blood clot or other solid mass, or an air bubble, can be delivered into the circulation through an IV and end up blocking a vessel; this is called embolism. Peripheral IVs have a low risk of embolism, since large solid masses cannot travel through a narrow catheter, and it is nearly impossible to inject air through a peripheral IV at a dangerous rate. The risk is greater with a central IV.

Air bubbles of less than 30 milliliters generally dissolve into the circulation harmlessly. A larger amount of air, if delivered all at once, can cause life-threatening damage to pulmonary circulation, or, if extremely large (3-8 milliliters per kilogram of body weight), can stop the heart.

One reason veins are preferred over arteries for intravascular administration is because the flow will pass through the lungs before passing through the body. Air bubbles can leave the blood through the lungs. A patient with a heart defect causing a right-to-left shunt is vulnerable to embolism from smaller amounts of air.

Fatality by air embolism is vanishingly rare, in part because it is also difficult to diagnose.

Saline

In medicine, *saline* is a solution of sodium chloride in sterile water, used commonly for intravenous infusion, rinsing contact lenses, and nasal irrigation or jala neti. Sodium chloride (NaCl) is ordinary salt. Saline solutions are available in various concentrations for different purposes.

Normal saline is the solution of 0.9% w/v of NaCl. It contains 154 mEq/L of Na+ and Cl. It has a slightly higher degree of osmolality (i.e. more solute per liter) compared to blood (hence, though it is referred to as being isotonic with blood in clinical contexts, this is a technical inaccuracy), about 300 mOsm/L. Normal saline (NS) is therefore used frequently in intravenous drips (IVs) for patients who cannot take fluids orally and have developed severe dehydration. Normal saline is typically the first fluid used when dehydration is severe

enough to threaten the adequacy of blood circulation and is the safest fluid to give quickly in large volumes.

Other concentrations of saline are frequently used for other purposes, such as supplying extra water to a dehydrated patient or supplying the daily water and salt needs ("maintenance" needs) of a patient who is unable to take them by mouth. Because infusing a solution of low osmolality can cause problems, intravenous solutions with reduced saline concentrations typically have dextrose (glucose) added to maintain a safe osmolality while providing less sodium chloride. As the molecular weight (MW) of dextrose is greater, this has the same osmolality as normal saline but contributes less sodium to the circulation. Because dextrose monohydrate (MW 198 in contrast to MW 180 for glucose) is the commercial form of dextrose used in these preparations, 5% dextrose actually contains only 4.5 g/dL of glucose.

Concentrations commonly used include

1. Half-normal saline (0.45% NaCl), often with "D5" (5% dextrose), contains 77 mEq/L of Na and Cl and 4.5 g/L glucose.
2. Quarter-normal saline (0.22% NaCl) has 39 mEq/L of Na and Cl and always contains 5% dextrose for osmolality reasons.
3. Dextrose (glucose) 4% in 0.18% saline is used sometimes for maintenance replacement.

The amount of normal saline infused depends largely on the needs of the patient (e.g. ongoing diarrhoea or heart failure) but is typically between 1.5 and 3 litres a day for an adult.

Rinsing with a saline solution is also a common remedy for a toothache or mouth pain.

See also

- Intravenous therapy

Medicinal herbs and fungi

Essential oils

Plant oils

Types

Vegetable fats

Essential oil

Macerated

Uses

Drying oil - Oil paint, Cooking oil, Fuel - Biodiesel, Aromatherapy

Components

Saturated fat, Monounsaturated fat, Polyunsaturated fat, Trans fat

An *essential oil* is a concentrated, hydrophobic liquid containing volatile aromatic compounds from plants. It is produced by distillation. Other extraction processes to obtain aromatic plant compounds include expression, or solvent extraction. Essential oils are used in perfumery, aromatherapy, cosmetics, incense, for flavoring food and drink, and to a lesser extent, in medicine and household cleaning products. They are valuable commodities to the fragrance and flavorant industries.

Essential oil is also known as *volatile oil* and *ethereal oil*. It may also be referred to as "oil of" the raw plant material from which it was extracted, such as oil of clove. The term *essential* is intended to indicate that the oil is the fragrant essence of the plant from which it is extracted and not in the more common sense of being indispensable. It is not to be confused with essential fatty acids.

Medical use of vegetable oils has a long and distinguished history. Many oils that are use medicinally are *essential oils*, which are distilled rather than pressed or otherwise extracted. Medical properties claimed by those who sell medicinal oils vary from skin treatments to remedies for cancer, and are often based on historical use of these oils for these purposes. Such claims are now subject to regulation in most countries, and have grown correspondingly more vague, to stay within these regulations.

Interest in such uses of essential oils has enjoyed a revival in recent decades, with the popularity of aromatherapy, in which oils are heated and volatilized.

Production

Distillation

Today, most common essential oils, such as lavender, peppermint, and eucalyptus, are distilled. Raw plant material, consisting of the flowers, leaves, wood, bark, roots, seeds, or peel, is put into an alembic (distillation apparatus) over water, As the water is heated the steam passes through the plant material, vaporizing the volatile compounds. The vapors flow through a coil where they condense back to liquid, which is then collected in the receiving vessel.

Most oils are distilled in a single process. One exception is Ylang-ylang (Cananga odorata), which takes 22 hours to complete through a Fractional distillation.

The water recondensed from the distillation process is referred to as a hydrosol, hydrolat, herbal distillate or plant water essence, which may be sold as another fragrant product. Popular hydrosols are rose water, lavender water, lemon balm, clary sage and orange blossom water. The use of herbal distillates in cosmetics is increasing. Some plant hydrosols have unpleasant smells and are therefore not sold.

Expression

Most citrus peel oils are usually expressed mechanically, or cold-pressed. Due to the large quantities of oil in citrus peel and the relatively low cost to grow and harvest the raw materials, citrus-fruit oils are cheaper than most other essential oils. Lemon or sweet orange oils that are obtained as by-products of the commercial citrus industry are even cheaper.

Prior to the discovery of distillation, essential oils (EO) were extracted by pressing.

Solvent extraction

Most flowers contain very little volatile oil to undergo expression and their chemical components are too delicate and easily denatured by the high heat used in steam distillation. Instead, a solvent such as hexane or supercritical carbon dioxide is used to extract the oils. Extracts from hexane and other hydrophobic solvent are called concretes, which is mixture of essential oil, waxes, resins, and other lipophilic (oil soluble) plant material.

Although highly fragrant, concretes contain large quantities of non-fragrant waxes and resins. As such another solvent, often ethyl alcohol, which only dissolves the fragrant low-molecular weight compounds is used to extract the fragrant oil from the concrete. The alcohol is removed by a second distillation, leaving behind the absolute.

In supercritical fluid extraction, supercritical carbon dioxide is used as a solvent. This method has many benefits, including avoiding petrochemical residues in the product. It does not obtain an absolute directly. The supercritical carbon dioxide will extract both the waxes and the essential oils that make up the concrete. Subsequent processing with liquid carbon

dioxide, achieved in the same extractor by merely lowering the extraction temperature, will separate the waxes from the essential oils. This lower temperature process prevents the decomposition and denaturing of compounds and provides for a superior product. When the extraction is complete, the pressure is reduced to ambient and the carbon dioxide reverts back to a gas, leaving no residue. Although supercritical carbon dioxide is also used for making decaffeinated coffee, the actual process is different.

Production quantities

Estimates of total production of essential oils are difficult to obtain. One estimate, compiled from data in 1989. 1990 and 1994 from various sources gives the following total production, in tonnes, of essential oils for which more than 1,000 tonnes were produced.[1]

Oil, Tonnes

- Sweet orange 12,000
- Mentha arvensis 4,800
- Peppermint **3,200**
- Cedarwood 2,600
- Lemon 2,300
- Eucalyptus globulus 2,070
- Litsea cubeba 2,000
- Clove (leaf) 2,000
- Spearmint 1,300

Essential oil use in aromatherapy

Aromatherapy is a form of herbal medicine, in which healing effects are ascribed to the aromatic compounds in essential oils and other plant extracts. Many common essential oils have medicinal properties that have been applied in folk medicine since ancient times and are still widely used today. For example, many essential oils have antiseptic properties, though some are stronger than others. In addition, many have an uplifting effect on the mind, though different essential oils have different properties.

Solvents

Essential oils are usually lipophilic compounds. It thus has been found that alcohols, such as methanol and ethanol (primarily 100% concentrations), or organic solvents, such as acetone, are the best diluents to be used for dilution. Water is not recommended as water and fats do not dissolve in one another, although oil dilution in water can be achieved at extremely low concentrations of oil, and depending on the viscosity of the oil.

Raw Materials

Essential oils are derived from various parts of plants. Some, like orange oil, are derived from any of several parts of the plant.

Berries

- Allspice
Juniper

Seeds

- Almond
Anise
Celery
Cumin
Nutmeg oil

Bark

- Cassia
Cinnamon

Wood

- Camphor
Cedar
Rosewood
Sandalwood

Rhizome

- Ginger

Leaves

- Basil
Bay leaf
Cinnamon
Common sage
Eucalyptus
Lemon grass
Melaleuca
Oregano
Patchouli
Peppermint

Pine
Rosemary
Spearmint
Tea tree
Thyme
Wintergreen

Resin

- Frankincense

Myrrh

Flowers

- Chamomile

Clary sage
Clove
Geranium
Hyssop
Jasmine
Lavender
Manuka
Marjoram
Orange
Rose
Ylang-ylang

Peel

- Bergamot

Grapefruit
Lemon
Lime
Orange
Tangerine

Root

- Valerian

Rose oil

The most well-known essential oil is probably Rose oil, produced from Rosa damascena and Rosa centifolia. Steam-distilled rose oil is known as "rose otto" or "attar of roses" while oil which is solvent-extracted is known as "rose absolute".

Dangers

Because of their concentrated nature, EO's generally should not be applied directly to the skin in their undiluted or "neat" form. Some can cause severe irritation or provoke an allergic reaction. Instead, essential oil should be applied with a plants oils or other fats (carrier oil), such as olive, hazelnut, or any other "soft" oil. Common ratio of essential oil disbursed in a carrier oil is 0.5–3% (most less than 10%) and depends on its purpose. Some EO's including many of the citrus peel oils, are photosensitizers, increasing the skin's reaction to sunlight and making it more likely to burn.

Industrial users of essential oils should consult the material safety data sheets (MSDS) to determine the hazards and handling requirements of particular oils.

Pesticide residues

There is some concern about pesticide residues in EO's, particularly those used therapeutically. For this reason, many practitioners of aromatherapy choose to buy organically produced oils.

Ingestion

While some advocate the ingestion of essential oils for therapeutic purposes, this should never be done except under the supervision of a professional who is licensed to prescribe such treatment. Some very common EO's such as Eucalyptus are extremely toxic internally. Pharmacopoeia standards for medicinal oils should be heeded. EO's should always be kept out of the reach of children. Some oils can be toxic to some domestic animals, cats in particular. Owners must ensure that their pets do not come into contact with potentially harmful essential oils.[2]

Smoke

The smoke from burning essential oils may contain potential carcinogens, such as polycyclic aromatic hydrocarbons (PAHs). Essential oils are naturally high in volatile organic compounds (VOCs). The internal use of essential oils should be fully avoided during pregnancy without consulting with a licensed professional, as some can be abortifacients in dose 0.5–10 ml.

Toxicology

LD50 of most EO or their main components are 0.5-10 g/kg (orally or skin test).

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Herbal and fungal hallucinogens

Agaricales | Amanita muscaria | Ayahuasca | Ergot | Morning glory | **Nicotiana rustica** | Peyote | Psychedelic mushroom | Soma | Tobacco

Agaricales

Scientific classification

Kingdom: Fungi
Division: Basidiomycota
Class: Homobasidiomycetes
Order: *Agaricales*

Families

Agaricaceae
Amanitaceae
Bolbitiaceae
Cortinariaceae
Crepidotaceae
Entolomataceae
Fistulinaceae
Hygrophoraceae
Omphalotaceae
Pleurotaceae
Pluteaceae
Podaxaceae
Psathyrellaceae
Schizophyllaceae
Strophariaceae
Tricholomataceae

The order *Agaricales*, also known as *gilled mushrooms* (for their distinctive gills), or *euagarics*, contains some of the most familiar types of mushrooms. The order has about 4,000 species, or one quarter of all known homobasidiomycetes. They range from the ubiquitous button mushroom to the deadly destroying angel and the hallucinogenic fly agaric to the bioluminescent jack-o-lantern mushroom.

Classification

Some notable fungi with gill-like structures, such as chanterelles, have long been recognised as being substantially different to usual Agaricales. Interestingly, molecular studies are showing other groups as being more divergent than previously thought, such as

the genera Russula and Lactarius belonging to a separate order Russulales, and other gilled fungi, including such species as Paxillus involutus and Hygrophoropsis aurantiaca showing a closer affinity with Boletes in the order Boletales.

Also, some other quite distinctive fungi, the puffballs and the Beefsteak fungus have been recently been shown lie within the Agaricales.

Distribution and habitat

Agarics are ubiquitous, being found across all continents except Antarctica. Although all are terrestrial, their habitats include all types of woodland and grassland, varying largely from one species to another.

Characteristics

Basidiocarps of the agarics are typically fleshy, with a stipe, often called a stem or stalkm a pileus (or cap) and lamellae (or gills), where basidiospores are stored. This is indeed the stereotyped structure of what we would call a mushroom or toadstool.

Life cycle

The agarics' life cycle is very much representative of the basiodiomycetes. Clamp connections are present in the dikaryons of several species, but that is not always the case.

Propagation

The agarics always have their basiodiospores ejected from the basidium into the area between gill edges. The spores are then let fall to the ground or carried by the wind.

Amanita muscaria

Amanita muscaria
Conservation status: Secure

Scientific classification

Kingdom: Fungi
Division: Basidiomycota
Class: Homobasidiomycetae
Subclass: Hymenomycetes
Order: Agaricales
Family: Amanitaceae
Genus: Amanita
Species: *A. muscaria*

Binomial name

Amanita muscaria

(Linnaeus) Hook.

Amanita muscaria, commonly called *fly agaric* or less often *fly mushroom*, is a basidiomycete mushroom of the genus Amanita. The original white-spotted red toadstool, it is one of the most recognizable mushrooms and is widely used in popular culture. Though it is generally considered poisonous, Amanita muscaria is otherwise famed for its hallucinogenic properties.

The common names in English, "fly agaric", and German, "Fliegenpilz", come from its European use as an insecticide, sprinkled in milk. This was known to Linnaeus who gave it the name *"Agaricus muscarius"*, the specific name deriving from Latin musca meaning "fly". The flykilling agent is now known to be ibotenic acid[1].

A mushroom that is native to both Europe and North America, Amanita muscaria has been unintentionally conveyed to many countries in the southern hemisphere, generally as a symbiont with pine plantations, and is now a true cosmopolitan species.

Description

Amanita muscaria is a large distinctive mushroom, generally common and numerous where it grows, often being found in groups with basidiocarps in all stages of development. Fully grown, the bright red cap is usually around 8-20 cm (3-8 in) in diameter, though sometimes larger ones are found, and is covered with numerous small white to yellow flecks (warts). It is worth noting that the red colour may fade after rain and in older mushrooms. The warts are remnants of the universal veil, a membrane that encloses the entire mushroom when it is still very young. The gills are white, as is the sporeprint. The stem is white, 5-20 cm high (approximately 2-8 inches), with a basal bulb that bears universal veil remnants, in the form of a ragged collar or group of more or less distinct rings or ruffs that circles the base of the stalk (or stipe). The white ring can be quite wide and flaccid. There is generally no associated smell.[2]

Fly agaric fruiting bodies emerge from the soil looking like a white egg, covered in the white warty material of the universal veil. As the fungus grows, the red colour appears through the broken veil, and the cap changes from bell-shaped to hemispherical and finally flattening in mature specimens[3].

Though very distinctive, the fly agaric has been mistaken for other yellow to red species in the Americas such as Armillaria cf. mellea and the edible Amanita basii, a Mexican species similar to A. caesarea of Europe. Poison control centers in the U.S. and Canada are aware that "amarillo" is a common name of caesarea-like species in Mexico, not just the Spanish for 'yellow'.

Amanita caesarea can be distinguished as it has an entire orange red cap, lacking the numerous white warty spots of the fly agaric. Furthermore the stem, gills and ring are bright yellow, not white[4]. Finally the volva is a distinct white bag, not broken into scales[5].

In Australia, the introduced fly agaric may be confused with the local Amanita xanthocephala, which grows in association with Eucalypts. This species also generally lacks the white warts of A. muscaria and bears no ring.

Classification

Amanita muscaria is a member of the large genus Amanita, of which there are many deadly poisonous as well as some edible species. The highly poisonous Panther Cap (Amanita pantherina) is somewhat similar in appearance though brown rather than red. Other red Amanitas include the previously mentioned edible Caesar's mushroom (Amanita caesarea).

Two recent molecular studies show that Amanita muscaria's close relatives in the genus appear to be Amanita gemmata, A. farinosa and A. roseitincta.[6][7]

Varieties

Other varieties have similar appearance to var. muscaria, but differ most conspicuously in cap colour:

- Var. *alba*, an uncommon fungus, has a white to silvery white cap with white warts but otherwise similar to the usual form. Fruiting in August and September, it is restricted to mixed coniferous and deciduous forests in northern North America.[8]
- Var. *americana* has a yellow or yellow-orange cap
- Var. *aureola* is found in southern Europe, and has an orange cap.
- Var. *flavivolvata* is red, with yellow warts, and occurs in the western regions of the North American continent, from southern Alaska down through the Rocky Mountains, Costa Rica to at least Andean Colombia. It contains similar poisons to var. muscaria.
- Var. *formosa*, found in Europe, has an orange-yellow cap with yellowish or tan warts and stem.
- Var. *guessowii* is yellow to orange, with center of cap more orange or reddish orange than the outer part, apparently restricted to northeastern North America, from Newfoundland and Quebec down to Tennessee.
- Var. *persicina* is pinkish to orangish "melon" colored with poorly formed or absent remnants of universal veil on the stem and vasal bulb, known from the Southeastern Coastal areas of the U.S.A, described in 1977[9].
- Var. *regalis*, from Scandinavia and Alaska[10], is liver-brown and has yellow warts. It appears to be uniformly distinctive and some authorities treat it as a separate species (A. regalis) though at least one DNA study does not support this.[11]

Distribution and habitat

Amanita muscaria is a cosmopolitan mushroom, found naturally in birch, pine, spruce and fir woodlands across the northern hemisphere from the British Isles to Siberia, and North America. It has been widely transported into the southern hemisphere, including Australia,[12] New Zealand, South Africa[13] and South America, where it usually occurs under introduced pine trees.

In Australia it appears to have formed new associations with southern beech (Nothofagus) in Tasmania and Victoria and invading native rainforest.[14]

When imported to a new country, A. muscaria can jump to native species (for example, Eucalyptus in Australia). It can then be exported with its new symbiont (for example, from Australia to Argentina).

A recent molecular study proposes an ancestral origin in the Siberian–Beringian region in the Tertiary period before radiating outwards across Asia, Europe and North America.[11]

Toxicity

Consuming more than about one gram of Amanita muscaria can cause nausea and a number of other effects, depending on dosage, ranging from twitching to drowsiness, cholinergic effects (lower blood pressure, increase sweat and saliva), visual distortions, mood changes, euphoria, relaxation, and hallucinations.

In near-fatal doses it causes swollen features and delirium, characterised by bouts of marked agitation followed by periods of quiet hallucination. Effects appear after around 60 minutes and typically peak within three hours, but certain effects can last for up to ten hours. The effect is highly variable and individuals can react quite differently to the same dose.

Deaths from A. muscaria are extremely rare. Fatal doses have occurred in North America (var. guessowii). The amount and ratio of chemical compounds per mushroom varies widely from region to region, season to season, further confusing the issue. Many older books list it as deadly, giving the impression that it is far more toxic than it really is. The vast majority of mushroom poisoning fatalities (90% or more) are from having eaten either the greenish to yellowish to brownish mottled death cap (Amanita phalloides) or one of the destroying angels (Amanita virosa), several overall white Amanita species.

The toxic substances of A. muscaria are water soluble and susceptible to heat. The mushroom can be at least partly de-toxified by thoroughly parboiling or leaching it in boiling water. According to some sources[1], once detoxified, the mushroom becomes edible.

Chemistry

The mushroom contains a number of psychoactive agents: ibotenic acid, muscimol, muscazone and muscarine, of which muscimol (3hydroxy-5-aminomethy-1 isoxazole, an unsaturated cyclic hydroxamic acid) is the most significant. Muscarine, discovered in 1869, was long thought to be the active hallucinogenic agent in A. muscaria until late 1960s, when scientists recognized it as ibotenic acid and muscimol. Some users cook the mushroom before ingestion, because it is said that the ibotenic acid turns into muscimol under this heat.

This supposedly removes several unpleasant side effects due to the conversion of the much more toxic ibotenic acid into muscimol.

Muscarine binds with Muscarinic acetylcholine receptor and lead to the excitation of the neurons bearing these receptors.

Psychoactive properties

Although the fly agaric is not related to other psychoactive fungi such as the Psilocybe species, it has been used as an entheogen in rituals to communicate to the spirit world, largely in Siberia, with some reported incidents elsewhere in the northern hemisphere. Mesoamericans never consumed fly agaric for religion, but instead use Psilocybe. Psilocybe and Amanita are not chemically related with regard to their psychoactive properties and therefore produce markedly different psychoactive effects.[15]

The active ingredient is excreted in the urine of those consuming the mushrooms, and it has sometimes been the practice for a shaman to consume the mushrooms, and the rest of the tribe to drink his urine: the shaman, in effect, partially detoxifying the drug (the sweat- and twitch-causing muscarine is absent in the urine)[16]. This was also not an uncommon practice in Siberia, where the poor would consume the urine of the wealthy, who could afford to buy the mushrooms. If a fly agaric is eaten, it is usually not fresh, but in its sun-dried form, where the hallucinogenic chemicals are more concentrated (ibotenic acid converted to the more stable and far less poisonous muscimol).

The notion that Nordic Vikings used Amanita muscaria to produce their berserker rages was first suggested by the Swedish professor Samuel Ödman in 1784.[17] Ödman based his theories on reports about the use of fly agaric among Siberian shamans. The notion has become widespread since the 19th century, but no contemporary sources mention this use or anything similar in their description of berserkers. Today, it is generally considered an urban legend or at best speculation that cannot be proven.

Mythology and religion

Koryak Siberians have a story about the fly agaric (wapaq) which enabled Big Raven to carry a whale to its home. In the story, the deity Vahiyinin ("Existence") spat onto earth, and his spittle became the wapaq, and his saliva becomes the warts. After experiencing the power of the wapaq, Raven was so exhilarated that he told it to grow forever on earth so his children, the people, can learn from it.Finno-Ugric peoples have traditionally used Amanita muscaria as entheogen.

Amanita muscaria is widely thought to be the Soma talked about in Rig Veda of India,[15] and is less often also thought to be the amrita talked about in Buddhist scriptures.[18]

John Marco Allegro argues in The Sacred Mushroom and the Cross that the Christian religion is derived from a sex and psychedelic mushroom cult.[19]

Ethnobotanist and ethnomycologist Giorgio Samorini suggests in his book "Animals and Psychedelics" a symbiotic relationship between toads, flies and fly agaric. Flies, after a lick of Amanita Muscaria become inebriated and delirious prey for hungry toads that may have learned this, therefore hanging out around toadstools. This relationship within nature

illuminates an etymological keystone and example of zoopharmacognosy. This would also provide further biosemiotic insight into the ancient mystery of toads, flies and mushrooms appearing together in popular mythology and fairy lore.

The British writer Robert Graves theorizes in a preface to his book, The Greek Myths, that the Dionysian saturnalias were conducted under the influence of this mushroom.[20]

Legality

Amanita muscaria is un-scheduled in the United States. Any sales of Amanita muscaria for human ingestion are regulated by the FDA.

In the United Kingdom, the sale of Amanita muscaria is illegal.

Popular culture

The red-and-white spotted toadstool is a common image in popular culture; a partly grown Amanita muscaria, as shown left, is clearly the fungus which this icon is based on.

Children's culture

Garden ornaments, and children's picture books depicting gnomes and fairies very often show fly agaric mushrooms used as seats, or homes; it is rather uncommon for any other mushroom to be shown in this role. How this artistic convention arose is not known.

Art

The mushroom is mentioned in the song "The Flowers of Guatemala" by the American band R.E.M., providing the song's central image.

Santa Claus

The ethnobotanist Jonathan Ott has suggested that the idea of Santa Claus and the tradition of hanging stockings over the fireplace is based centrally upon the fly agaric mushroom itself.[21] With its generally red and white color scheme, he argues that Santa Claus's suit is related to the mushroom. He also draws parallels with flying reindeer: reindeer are said to enjoy the mushroom because of its euphoric results, and therefore prance around in a hallucinogenic after-effect.[22] A direct connection to Santa Claus is not very likely, as until the 20th century, the red-and-white Santa suit familiar today was not especially common (see also: Origins of Santa Claus). One scholar researching possible links between religious myths and the red mushroom notes, "If Santa Claus had but one eye [like Odin], or if magic urine had been a part of his legend, his connection to the Amanita muscaria would be much easier to believe."[23]

Ott also speculates about Santa's bag of toys. According to historians, ancient Siberia was one of the first civilizations to use fly agaric in practice. The Siberian hut, or yurt, is equipped with a smokehole at the top. Ott suggests that a shaman entered the yurt through the

smokehole with a sack of mushrooms in his hand, to be placed in stockings over the fireplace where they could be dried for celebratory use.

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Ayahuasca

The widely used Quechua name *ayahuasca* (pronounced [a.ja.Èwa.ska]) has two highly interrelated yet distinct meanings and referents: 1) an Amazonian giant vine native to the rainforest containing various harmala alkaloids, generally Banisteriopsis caapi, and, by extension, 2) pharmacologically complex psychoactive infusions prepared from it for shamanic, folk-medicinal, and religious purposes. Sections of vine are macerated and boiled alone or with leaves from any of a large number of other plants, including Psychotria viridis (chakruna in Quechua) or Diplopterys cabrerana (also known as chacropanga). The resulting brew contains MAO inhibiting harmala alkaloids and the powerful hallucinogenic alkaloid N,N-dimethyltryptamine (DMT), a psychedelic which is active orally only when combined with an MAOI. Harmala alkaloids in Banisteriopsis caapi serve as MAOIs in Ayahuasca. Western brews sometimes substitute plant sources such as Syrian Rue or other harmala containing plants in lieu of the Banisteriopsis caapi vine, but the vine itself is always central to traditional usage.

Brews are also made with no DMT-containing plants; sometimes they are made with plants such as Justicia pectoralis, Brugmansia and sometimes made with no plants other than the ayahuasca vine itself. Tobacco is a common additive in traditional brews. The potency of this brew varies radically from one batch to the next, both in strength and psychoactive effect, based mainly on the skill of the shaman or brewer, as well as other admixtures sometimes added. Natural variations in plant alkaloid content and profiles also affect the

final concentration of alkaloids in the brew, and the physical act of cooking may also serve to modify the alkaloid profile of harmala alkaloids.[1][2]

Individual polymorphisms in the cytochrome P450-2D6 enzyme affects the ability of individuals to metabolize harmine.[3] Some natural tolerance to the regular use of Ayahuasca (e.g. once weekly) may be seen as an upregulation of the serotonergic system.[4] A phase 1 pharmacokinetic study on Ayahuasca (as Hoasca) with 15 volunteers was conducted in 1993, during the Hoasca Project.[5] A review of the Hoasca Project has been published.[6]

Names

- "ayahuasca" or "daime" in Brazil

"yagé" or "yajé" (both pronounced [ja.'he]) in Colombia; popularized in English by the beat generation writers William S. Burroughs and Allen Ginsberg in The Yage Letters.

"ayahuasca" or "ayawaska" in Ecuador, Bolivia and Peru, also to a lesser extent in Brazil ("vine of the dead" or "vine of souls": in Quechua, aya means "spirit," "ancestor," or "dead person," while waska means "vine" or "rope"). The name is properly that of the plant B. caapi, one of the primary sources of beta-carbolines for the brew.

"natem" amongst the indigenous Shuar people of Peru.

It should be noted that the spelling ayahuasca is the hispanicized version of the name; many Quechua or Aymara speakers would prefer the spelling ayawaska. In the central andeans of Perú Ayacwasca means :"Ayac" (spirit or dead) and "Wasca" (vine, cord or rope)

Usage

Ayahuasca is used in largely as a religious sacrament, no matter which culture it is associated with. Those who use ayahuasca in non-traditional contexts often align themselves with the philosophies and cosmolgies associated with ayahuasca shamanism, as practiced among indigenous peoples like the Urarina of Peruvian Amazonia.

While non-native users know of the spiritual applications of ayahuasca, a less well-known traditional usage focuses on the medicinal properties of ayahuasca. Its purgative properties are highly important (many refer to it as la Purga, "the purge"). The intense vomiting and occasional diarrhea it induces can clear the body of worms and other tropical parasites, and harmala alkaloids themselves have been shown to be anthelmintic[7]. Thus, this action is two-fold; a direct action on the parasites by these harmala alkaloids (particularly harmine in ayahuasca) works to kill the parasites, and parasites are expelled through the increased intestinal motility that is caused by these alkaloids.

Dietary taboos are almost always associated with the use of Ayahuasca; in the rainforest, these tend towards the purification of one's self- abstaining from spicy and heavily seasoned foods, fat, salt, caffeine, acidic foods (such as citrus) and sex before, after, or both before and after a ceremony. A diet low in foods containing tyramine is recommended, as the interaction of tyramine and MAOIs can lead to a hypertensive crisis. This extreme dietary specificity is largely a modern one, as most tyramine is produced as food ages, and is therefore not usually

a problem in traditional South American cultures. These dietary restrictions have developed as a means of making ayahuasca ingestion easier on the body, as well as having strong traditional and spiritual significance

Today, the name 'ayahuasca' can mean a variety of botanical concoctions containing one or more MAOIs and DMT or one of its chemical analogues. The synthetic pharmahuasca is sometimes called ayahuasca as well. In this usage, the DMT is generally considered the main psychoactive active ingredient, while the MAOI merely activates orally ingested DMT. However, most ayahuasqueros and others working with the brew claim the B. caapi vine to be the defining ingredient; according to them, it is not ayahuasca unless B. caapi is in the brew. The vine is considered to be the "spirit" of ayahuasca, the gatekeeper and guide to the otherworldly realms.

In some areas, it is even said that the chacruna or chaliponga admixtures are added only to make the brew taste sweeter. This is a strong indicator of the often wildly divergent intentions and cultural differences between the native ayahuasca-using cultures and psychedelics enthusiasts in other countries.

In modern Europe and North America, ayahuasca analogues are often prepared using non-traditional plants which contain the same alkaloids. For example, seeds of the Syrian rue plant are often used as a substitute for the ayawaska vine, and the DMT-rich Mimosa hostilis is used in place of chakruna. Australia has several indigenous plants which are popular among modern ayahuasqueros there, such as various DMT-rich species of Acacia.

In modern Western culture, entheogen users sometimes base concoctions off of Ayahuasca. When doing so, most often Rue or B. caapi are used with an alternative form of the DMT molecule, such as psilocin, or a non-DMT based hallucinogen such as mescaline. Nicknames such as Psilohuasca, Mush-rue-asca, or 'Shroom-a-huasca, for mushroom based mixtures, or Pedrohuasca (from the San Pedro Cactus, which contains mescaline) are often given to such brews. Such nicknames are by many considered innapropriate and culturally insensitive seeing as "huasca" means "vine" and none of the above are vines, nor do the psychedelic experimentalist trappings of such concoctions bear any resemblance to the medicinal use of Ayahuasca in its original cultural context. This is usually only done by experienced entheogen users who are more familiar with the chemicals and plants being used, as the uninformed combination of various neuro-chemicals can be dangerous.

It seems unlikely that Ayahuasca could ever emerge as a "street-drug", given the difficulty of making the tea and the intense experience it provides. Most Western users employ it almost exclusively for spiritual purposes, in line with both traditional, animist usage and organized churches such as the the Uniao do Vegetal (or UDV). A diet is almost always followed before use, including a day of fasting, to rid the body of tyramines and other contraindicated chemicals; a "dieta" is often followed as well, to spiritually cleanse the body before and after the experience. Most recreational drug users have never even heard of Ayahuasca, DMT or MAOIs, or the possibility of alterations to the shamanic brew.

Introduction to the West

Ayahuasca is mentioned in the writings of some of the earliest missionaries to South America, but it wasn't for some time that it became commonly known in the West. The early

missionary reports generally claim it as demonic, and great efforts were made by the Roman Catholic Church to stamp it out.

When originally researched in the 20th century, the active chemical constituent of Caapi was called telepathine, but it was found to be identical to a chemical already isolated from Peganum harmala and given the name harmaline.

William Burroughs sought yagé (still considered to be "telepathine") in the 1950s while traveling through South America, in the hopes that it could relieve or cure opiate addiction. The Yage Letters, written between Burroughs and Allen Ginsberg were probably the first major introduction of Ayahuasca to the West.

Ayahuasca was made more widely known by Terence and Dennis McKenna's experiences with Amazonian tribes as detailed in the book Invisible Landscape, which they co-authored. Their journey to the rainforest to search for Ayahuasca was spurred by their reading of Burroughs and Ginsberg. Dennis later extensively studied the pharmacology, botany, and chemistry of ayahuasca and oo-koo-he, which were the subjects of his master's thesis.

In Brazil, a number of modern religious movements based on the use of ayahuasca have emerged, the most famous of them being Santo Daime and the União do Vegetal (or UDV), usually in an animistic context that may be shamanistic or, more often, (as with Santo Daime and the UDV,) integrated with Christian. Both Santo Daime and União do Vegetal now have members and churches throughout the world.

Similarly, the US and Europe has started to see new religious groups born of experiences with ayahuasca. In the US a Wicca group, PaDeva, has become the first incorporated legal church with which ayahuasca is central to their beliefs.

Several notable celebrities have publicly discussed their use of ayahuasca, including Sting, Tori Amos, and Paul Simon (who wrote the song Spirit Voices about his experience with the brew in the Amazon).

Some "Westerners" have teamed up with "shamans" in the amazon rainforest regions and forming Ayahuasca "healing retreats" claiming that it can cure mental and physical illness and allow communication with the spirit world. This is not to say that all organizations catering to ayahuasca tourists are inherently bad, but one should be cautious. Though both anecdotal reporting and scientific studies affirm that ritualized use of ayahuasca can lead to the betterment of human mental and physical health, the monoamine oxidase inhibitor (MAOI) component of the brew is a powerful compound that interacts with many foods that some Westerners would not consider dangerous, from liver to Vegemite.

Wade Davis most notably acredited with the writting of The Serpent and The Rainbow wrote in addition to that book one entitled One River. Many examples of ayahuasca as used traditionally by the indigenous jungle tribes of the Amazon Basin are detailed through the book. "The smell and acrid taste was that of the entire jungle ground up and mixed with bile." [p.194]

Plant constituents

Traditional

Traditional Ayahuasca brews are always made with B. caapi as an MAOI, although DMT sources and other admixtures vary from region to region. There are several varieties of caapi, often known as different "colors", with varying effects, potencies, and uses.

DMT admixtures:

- Psychotria viridis (Chakruna) - leaves
- Diplopterys cabrerana (Chaliponga, Banisteriopsis rusbyana) - leaves
- Psychotria carthagensis (Amyruca) - leaves

Other common admixtures:

- Justicia pectoralis
- Brugmansia (Toé)
- Nicotiana rustica (Mapacho)
- Ilex guayusa, a relative of yerba mate

Western

Although traditional plant materials are often used, sources with similar chemical constituents are often substituted for the traditional ingredients.

MAOI:

- Harmal (Peganum harmala, Syrian Rue) - seeds
- Passion flower

DMT admixture sources:

- Acacia maidenii (Maiden's Wattle), Acacia phlebophylla, and other Acacias, most commonly employed in Australia - bark
- Anadenanthera peregrina, A. colubrina, A. excelsa, A. macrocarpa
- Mimosa hostilis (Jurema) - root bark - not traditionally employed with ayahuasca by any existing cultures, though likely it was in the past. Popular in Europe and North America.

Legal status

Internationally, DMT is a Schedule I drug under the Convention on Psychotropic Substances. The Commentary on the Convention on Psychotropic Substances notes, however, that the plant itself is excluded from international control[1]:

The cultivation of plants from which psychotropic substances are obtained is not controlled by the Vienna Convention. . . . Neither the crown (fruit, mescal button) of the Peyote cactus nor the roots of the plant Mimosa hostilis nor Psilocybe mushrooms themselves are included in Schedule 1, but only their respective principles, mescaline, DMT and psilocin.

A fax from the Secretary of the International Narcotics Control Board to the Netherlands Ministry of Public Health sent in 2001 goes on to state that "Consequently, preparations (e.g.decoctions) made of these plants, including ayahuasca are not under international control and, therefore, not subject to any of the articles of the 1971 Convention." [2]

The legal status of these plants in the United States is somewhat questionable. Ayahuasca plants and preparations are legal as they contain no scheduled chemicals. However, brews made using DMT containing plants are illegal since DMT is a Schedule I drug. That said, some

people are challenging this, using arguments similar to those used by peyotist religious sects, such as the Native American Church. A court case allowing Uniao do Vegetal to use the tea for religious purposes in the United States, Gonzales v. O Centro Espírita Beneficente União do Vegetal, was heard by the U.S. Supreme Court on November 1, 2005; the decision, released February 21st, 2006, allows the UDV to use the tea in its ceremonies persuant to the Religious Freedom Restoration Act.

Religious use in Brazil was legalized after two official inquiries into the tea in the mid-1980s, which concluded that ayahuasca is not a recreational drug and has valid spiritual uses. (more on the legal status of ayahuasca can be found in the Erowid vault on the legality of ayahuasca).

In France, Santo Daime won a court case allowing them to use the tea in early 2005; however, they were not allowed an exception for religious purposes, but rather for the simple reason that they did not perform chemical extractions to end up with pure DMT and harmala and the plants used were not scheduled. Four months after the court victory, the common ingredients of Ayahuasca as well as harmala were declared stupéfiants, or narcotic schedule I substances, making the tea and its ingredients illegal to use or possess. See [3] and [4] ***(French)*** for more information.

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Dimethyltryptamine

Chemical name 2-(1H-indol-3-yl)-N,N-dimethylethanamine

Chemical formula C***12***H***16***N***2***

Molar mass 188.27 g/mol

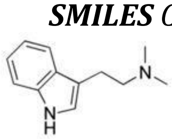
Density 1.099 g/ml

Melting point 49 °C and 74 °C (two different crystal structures)

Boiling point 160 °C at 0.8 hPa (reduced pressure)

CAS number 61-50-7

SMILES *CN(C)CCC1=CNC2=C1C=CC=C2*



Dimethyltryptamine(DMT), also known as Dimitri, and *N,N-dimethyltryptamine*, not to be confused with 5-MeO-DMT, is a psychedelic tryptamine, similar in structure to the neurotransmitter serotonin. DMT is created in small amounts by the human body during normal metabolism[1] by the enzyme Tryptamine-N-methyltransferase. Pure DMT at room temperature is a light pink, orange, or yellow waxy or crystalline solid. DMT was first chemically synthesized in 1931. It also occurs naturally in many species of plants. DMT-containing plants are used in several South American shamanic practices. It is one of the main active constituents of snuffs like yopo and of the drink ayahuasca.

DMT is not orally active unless it is combined with a monoamine oxidase inhibitor (MAOI), such as harmaline. Without an MAOI, the body quickly metabolizes orally-administered DMT, and it therefore has no hallucinogenic effect. Other means of ingestion such as smoking or injecting the drug, however, can produce powerful hallucinations and entheogenic activity for a short time (usually less than half an hour).

Hallucinogenic properties

DMT is a powerful psychoactive substance. If DMT is smoked, injected, or orally ingested with an MAOI, it can produce powerful entheogenic experiences including true hallucinations (perceived extensions of reality). A trip sitter is often employed to assist the drug user in staying physically and mentally healthy, and, in the case of smoked DMT, to catch the pipe when the user loses awareness of it.

Smoked: If DMT is smoked, the maximal effects last for a short period of time (5 - 30 minutes +). The onset after inhalation is very fast (less than 45 seconds) and maximal effects are reached within about a minute.

Insufflation: If DMT is insufflated (snorted through the nostrils) it will last slightly longer than if smoked and has less powerful effects.

Injection: Injected DMT produces an experience similar to inhalation in duration, intensity, and characteristics, although by some accounts it is more emotionally clinical (versus spiritual).

Oral ingestion: DMT, which is broken down by the digestive enzyme monoamine oxidase, is inactive if taken orally, unless combined with a monoamine oxidase inhibitor (MAOI). The traditional South American ayahuasca, or yage, is a decocted tea-like mixture containing DMT. There are a number of admixtures to this brew, but most commonly it is simply the leaves of Psychotria viridis (containing DMT), and the vine Banisteriopsis caapi (the MAOI). Other DMT containing plants, including Diplopterys cabrerana, are sometimes used in ayahuasca in different areas of South America. A common source in the western US is Reed canary grass or Phalaris arundinacea, and Harding grass or Phalaris aquatica. This invasive grass contains high levels of DMT and other alkaloids . Taken orally with an appropriate MAOI, DMT produces a long lasting (over 1 hour), slow onset experience. MAOIs should be used with extreme caution as they can have lethal complications with some prescription drugs, such as SSRI antidepressants, and some over-the-counter drugs.[2]

Induced DMT experiences can include profound time-dilation, visual and audio hallucinations, and other experiences that, by most firsthand accounts, defy verbal or visual description. Some users report intense erotic imagery and sensations and utilize the drug in

a ritual sexual context. Professor Alan Watts described the effects of DMT as "Load universe into cannon. Aim at brain. Fire."

In a 1988 study conducted at UNM, psychiatrist Rick Strassman found that approximately 20% of volunteers injected with high doses of DMT had experiences with a perceived alien entity. At least one subject reported sexual contact with these beings, and many others reported erotic experiences.

Excretion Urine

Legal status US: I CA: III UK: 1/A

Delivery Vaporized, injected, or orally in combination with MAO inhibitors

Recreational uses:
Euphoria
Psychedelic effects
Other uses:
Mystical Experience
Shamanic
spiritual/Religious
Contraindications:
Potentially fatal if currently taking an MAO-Inhibitor, such as many common anti-depressants
Do not use if suffering from Schizophrenia or similar conditions, or if such runs in your family.

Side Effects

When DMT is vaporized, the vapor produced is often felt to be very harsh on the lungs, especially if the dose contains impurities (commonly residue of sodium hydroxide or yellow/orange tannins from the plant sources), in extreme cases this can lead to retching and vomiting.

Chemistry

DMT is a derivative of tryptamine with two additional methyl groups at the amine nitrogen atom. DMT is often synthesized by the Speeter-Anthony synthesis from indole using oxalyl chloride, dimethylamine, and lithium aluminium hydride as reagents. DMT is usually used in its base form, but it is more stable as a salt, e.g. as a fumarate. In contrast to DMT's base, its salts are water-soluble. DMT in solution degrades relatively fast and should be stored protected from air and light in a freezer.

When solvents containing N,N-DMT are evaporated different purities of alkaloid and rates of evaporation produce different crystalline patterns. Depending upon purity, the formations produced can vary from small white raised bumps which may or may not appear to have a crystalline pattern within them to a fine pointed array of delicate crystalline

needled formations. Due to confinement in an evaporation container the extract shown in these photos became irregular tile-like shapes instead of the more common spoked circles at this purity. Ninety plus percent purity extract, when evaporated out of a solvent and depositing upon glass often produce small but highly defined white crystalline needles which when viewed under intense light will sparkle and upon close examination at high magnification can be seen to actually be without color and completely clear, if pure.

DMT which is in the form of a salt in dried Mimosa hostilis root bark is exceptionally free of plant fats which allows this substance to be extracted or isolated from the plant material by simply mixing powdered root bark into basified water which has had a base chemical such as NaOH dissolved into it to raise the pH of the watery mix to close to a pH of 13.5 and thereby converting the DMT salt into an alkaloid which can then be absorbed by a solvent. Once the root bark has been placed in basified water and stirred for a few minutes naphtha can be poured into the aqueous room temperature soup and stirred for twenty minutes or more which will allow the solvent to fairly selectively pull out a large portion of the alkaloid. Multiple half hour extractions are typical, stirring and extracting several times over until most of the alkaloid has been depleted through absorption into the solvent, combining the multiple fractions of solvent which have been separated from the aqueous mix each time by simply pouring the lower specific gravity solvent which is floating on top of the basified mix into a collection container and evaporated to net the alkaloid.

Speculations

Several speculative and as yet untested hypotheses suggest that endogenous DMT, produced in the human brain, is involved in certain psychological and neurological states. As DMT is naturally produced in small amounts in the brains and other tissues of humans, and other mammals[4], some believe it plays a role in promoting the visual effects of natural dreaming, near-death experiences and other mystical states. A biochemical mechanism for this was proposed by the medical researcher JC Callaway, who suggested in 1988 that DMT might be connected with visual dream phenomena, where brain DMT levels are periodically elevated to induce visual dreaming and possibly other natural states of mind.[3]

Dr. Rick Strassman, while conducting DMT research in the 1990's at the University of New Mexico, advanced the theory that a massive release of DMT from the pineal gland prior to death or near death was the cause of the near death experience phenomenon. Only two of his test subjects reported NDE-like audio or video hallucinations. His explanation for this was the possible lack of panic involved in the clinical setting and possible dosage differences between those administered and those encountered in actual NDE cases.

Several subjects also reported contact with 'other beings', alien like, insectoid and reptillian in nature, in technological environments[4] where the subjects were 'probed', 'tested' and sometimes even 'manipulated' by these 'beings', anyone is, regardless of interest for the subject, tempted to draw similarities between these experiences and the tales of alien encounters.

In the 1950s, the endogenous production of psychoactive agents was considered to be a potential explanation for the hallucinatory symptoms of some psychiatric diseases as the transmethylation hypothesis.[5]. Unfortunately, this hypothesis does not account for the natural presence of endogenous DMT in otherwise normal humans, not to mention rats and

other laboratory animals. The proposal by Dr. Callaway was the first to suggest a useful function for the endogenous production of DMT; i.e. to facilitate the visual phenomenon of normal dreaming.

Ethical concerns do not allow for the testing of this hypothesis in humans, as the biological samples must come from the living human brain. It is unknown if other animals actually do dream, as it is quite impossible to know this without their ability to tell us that they have had a dream, although REM sleep is highly correlated with dream sleep.

Writers on DMT include Terence McKenna and Jeremy Narby, though most scientists who study psychedelic drugs treat their writings with skepticism. McKenna writes of his experiences with DMT in which he encounters entities he describes as "Self-Transforming Machine Elves". McKenna believed DMT to be a tool that could be used to enhance communication and allow for communication with other-worldly entities. Other users report visitation from external intelligences attempting to impart information. These Machine Elf experiences are said to be shared by many DMT users. From a researcher's perspective, perhaps best known is Rick Strassman's DMT: The Spirit Molecule (ISBN 0-89281-927-8); Strassman also proposed that DMT is made in the pineal gland, although this is only speculation.

Legal status

DMT is classified in the United States as a Schedule I drug. In December of 2004, the Supreme Court lifted a stay thereby allowing the Brazil-based União do Vegetal (UDV) church to use a decoction containing DMT in their Christmas services that year. This decoction is a "tea" made from boiled leaves and vines, known as hoasca within the UDV, and ayahuasca in different cultures. In Gonzales v. O Centro Espírita Beneficente União do Vegetal, the Supreme Court heard arguments on November 1st, 2005 and unanimously ruled in February 2006 that the U.S. federal government must allow the UDV to import and consume the tea for religious ceremonies under the 1993 Religious Freedom Restoration Act.

DMT is classified in Canada as a Schedule III drug.

DMT, *along with most of its plant sources*, is classified in France as a stupéfiant.

DMT is classified in the United Kingdom as a Class A drug.

DMT creates legal dilemmas in many countries because possession is illegal but at the same time the drug is naturally present in the human body.

Culture

In Brazil there are a number of religious movements based on the use of Ayahuasca, usually in an animistic context that may be shamanistic, sometimes mixed with Christian imagery.

There are four main branches using DMT-MAOI based sacraments in Brasil:

1) Indigenous people - they are the oldest culture in the whole South America to use ayahuasca or analogue brews, such as the ones made from Jurema (Mimosa hostilis).

2) Santo Daime (Saint Giveme) and Barquinha (Lil'Boat) - the former was founded by a simple man, called Raimundo Irineu Serra, in the early 30s as an esoteric Christian religion with shamanic tendencies. The Barquinha cult was derived from this one.

3) União do Vegetal (Vegetable's Union) - another Christian ayahuasca religion, with a more Masonic tone. Today it's divided into at least three sects.

4) Neo-shamans - there are some shamanic facilitators in Brasil using ayahuasca and analogue brews in their rituals and séances, mainly in the State of Sao Paulo.

See also

- LSD
- Psilocybin

Notes

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Ergot

Scientific classification

Kingdom: Fungi
Division: Ascomycota
Class: Euascomycetes
Order: Hypocreales

Family: Clavicipitaceae
Genus: *Claviceps*

Species

About 50, including:
Claviceps africanum
Claviceps fusiformis
Claviceps paspali
Claviceps purpurea

Ergot is the common name of a fungus in the genus Claviceps. The fungus is parasitic on certain grains and grasses. The form the fungus takes to over-winter is called a sclerotium, and this small structure is what is usually referred to as 'ergot', although referring to the members of the Claviceps genus as 'ergot' is also correct. There are about 50 known species of Claviceps, most of them in the tropical regions. Economically important species are Claviceps purpurea (parasitic on grasses and cereals), C. fusiformis (on pearl millet, buffel grass), C. paspali (on dallis grass), and C. africana[1](on sorghum). C. purpurea can affect a number of cereals including rye (its most common host), triticale, wheat and barley. It affects oats only rarely.

There are three races or varieties of C. purpurea, differing in their host specifity: G1 - land grasses of open meadows and fields; G2 - grasses from moist, forest and mountain habitats; G3 (C. purpurea var. spartinae) - salt marsh grasses (Spartina, Distichlis).

Life cycle of the fungus

An *ergot kernel* called a sclerotium develops when a floret of flowering grass or cereal is infected by a spore of Claviceps fungus. The infection process mimicks a pollen grain growing into an ovary during fertilization. The fungus then destroys the plant ovary and attaches itself to a vascular bundle originally intended for seed nutrition. The first stage of ergot infection manifests itself as a white soft tissue (known as sphacelia) producing sugary honeydew, which often drops out of the grass florets. This honeydew contains millions of asexual spores (conidia) which are dispersed to other florets by insects. Later, the sphacelia convert into a hard dry sclerotium inside the husk of the floret. At this stage, alkaloids and lipids accumulate in the sclerotium.

Claviceps species from tropic and subtropic regions produce macro- and microconidia in their honeydew. Macroconidia differ in shape and size between the species, whereas microconidia are rather uniform, oval to globose (5x3um). Macroconidia are able to produce secondary conidia. A germ tube emerges from a macroconidium through the surface of a honeydew drop and a secondary conidium of the oval to pearlike shape is formed to which the contents of the original macroconidium migrates. Secondary conidia form white frost-like surface on honeydew drops and are spread by wind. No such process occurs in Claviceps purpurea, Claviceps grohii, Claviceps nigricans and Claviceps zizaniae, all from North temperate regions.

When a mature sclerotium drops to the ground, the fungus remains dormant until proper conditions trigger its fruiting phase (onset of spring, rain period, etc.). It germinates, forming one or several fruiting bodies with head and stipe, variously colored (resembling a tiny mushroom). In the head, threadlike sexual spores are formed, which are ejected simultaneously, when suitable grass hosts are flowering. Ergot infection causes a reduction in the yield and quality of grain and hay produced, and if infected grain or hay is fed to livestock it may cause a disease called ergotism.

Black and protruding sclerotia of C. purpurea are well known. However, many tropical ergots have brown or greyish sclerotia, mimicking the shape of the host seed. For this reason, the infection is often overlooked.

Effects on humans and animals

Ergot contains alkaloids of the ergoline group, which have a wide range of activities including effects on circulation and neurotransmission. Ergotism is the name for the collection of symptoms a human or animal has when it has ingested (too much of) this fungus. Ergotism went also under the name "St. Anthony's fire" hinting at burning sensations in the limbs. Another effect of ergot alkaloids is vasoconstriction, therefore ergotism may lead to gangrene and loss of the limbs due to limited blood circulation. This may also cause insanity, convulsions, or death, due to limited circulation to the brain. Other symptoms include strong uterine contractions, nausea, seizures, and unconsciousness. Monks of the order of St. Anthony the Great specialized in treating ergotism victims with balms containing tranquilizing and blood circulation-stimulating plants; they were also skilled in amputations. Entire villages have been known to suffer ergotism after the village bakery used infected grain.

In addition to ergot alkaloids, Claviceps paspali also produces tremorgens (paspalitrem) causing "paspalum staggers" in cattle.

Historically, controlled doses of ergot were used to induce abortions and to stop maternal bleeding after childbirth, but simple ergot extract is no longer used as a pharmaceutical.

Among those who studied ergot and its derivatives was Albert Hofmann, whose experiments led to the discovery of LSD, a powerfully hallucinogenic ergot derivative that affects the serotonin system. Contrary to some rumors, ergot contains no LSD, but there are links between the two substances:

- LSD was first synthesised during research on the active ingredients of ergot.
- Lysergic acid, a raw material used in the synthesis of LSD, was and is still prepared from ergot.

Speculations

The disease cycle of the ergot fungus was first described in the 1800s, but the connection with ergot and epidemics among people and animals was known several hundred years before that.

Human poisoning due to the consumption of rye bread made from ergot-infected grain was common in Europe in the Middle Ages. The phenomenon known as Dancing mania has been blamed on accidental consumption of the fungus.

It has also been posited — though speculatively — that the Salem Witch Trials were initiated by young women who had consumed ergot-tainted rye. The Great Fear in France during the Revolution has also been linked by some historians to the influence of ergot. Most famously, ergot intoxicated a whole French village in 1951, at Pont-Saint-Esprit.

Kykeon, the beverage consumed by participants in the ancient Greek mystery of Eleusinian Mysteries, might have been based on hallucinogens from ergot.

Nowadays, rye grain is infected repeatedly to produce ergot.

Morning glory

Morning glory is a common name for a number of species of flowering plants in the family the Convolvulaceae, belonging to the following genera:

- Calystegia

Convolvulus
Ipomoea
Merremia
Rivea

As the name implies, morning glory flowers, which are funnel-shaped, open at morning time, allowing them to be pollinated by hummingbirds, butterflies, bees and other daytime insects and birds, as well as Hawkmoth at dusk for longer blooming variants. The flower typically lasts for a single morning and dies in the afternoon. New flowers bloom each day. The flowers usually start to fade a couple of hours before the petals start showing visible curling. They prefer full sun throughout the day, and mesic soils. In cultivation, most are treated as perennial plants in tropical areas, and as annual plants in colder climates, but some species tolerate winter cold.

Morning glory is also called *asagao* (in Japanese, a compound of asa "morning" and T kao "face"). A rare brownish-coloured variant known as Danjuro is very popular. It was first known in China for its medicinal uses, due to the laxative properties of its seeds. It was introduced to the Japanese in the 9th century, and they were first to cultivate it as an ornament. During the Edo Period, it became a very popular ornamental flower. Aztec priests in Mexico were also known to use the plant's hallucinogenic properties to commune with their gods.

Ancient Mesoamerican civilizations used it to coagulate rubber latex to produce bouncing rubber balls. The sulphur in the Morning Glory vine served to vulcanize the rubber; a process which pre-dates the Charles Goodyear discovery by over 1000 years.

Because of their fast growth, twining habit, attractive flowers, and tolerance for poor, dry soils, some morning glories are excellent vines for creating summer shade on building walls when trellised, thus keeping the building cooler and reducing air condtioning costs.

Culinary use

Ipomoea aquatica, known as water teeth, water morning-glory, water convolvulus or swamp cabbage, is popularly used as a green vegetable especially in East and Southeast Asian cuisines.

Recreational use

The seeds of many species of morning glory contain d-lysergic acid amide, ergoline alkaloids better known as LSA. Seeds of I. violacea and R. corymbosa are used as hallucinogens. They are about 5% to 10% as potent as LSD. To discourage morning glory's use as hallucinogenic drugs, some commercial seed producers have started treating seeds with a chemical that will not wash off. This chemical has been known to cause vomiting, nausea and abdominal pain. Typically some form of a warning or notice is printed on the package if seeds have been treated.

Peyote

Scientific classification

Kingdom: Plantae
Division: Magnoliophyta
Class: Magnoliopsida
Order: Caryophyllales
Family: Cactaceae
Genus: Lophophora
Species: *L. williamsii*

Binomial name Lophophora williamsii (Lem.) J. Coult.

Peyote (Lophophora williamsii) is a small, spineless cactus whose native region extends from the southwestern United States (including the states of Texas and New Mexico) through central Mexico. It has been used for centuries for the psychedelic effects experienced when it is ingested.

Plant

The cactus flowers sporadically, producing small pink fruit, similar in appearance to a chili pepper, which can be very delectable and sweet-tasting when eaten. The seeds are small and black, requiring hot and humid conditions to germinate, one of the reasons this tranquil plant is becoming rare in its natural habitat. Numbers are reducing due to harvesting for commercial purposes. Peyote contains a large spectrum of phenethylamine alkaloids, the principal of which is mescaline. All Lophophora species are extremely slow growing, often taking up to thirty years to reach flowering age (at about the size of a golf ball, not including root) in the wild. Human cultivated specimens grow considerably faster, usually taking from

six to ten years to go from seedling to mature flowering adult. Due to this slow growth and over-harvesting by collectors, peyote is considered to be in danger of extinction in the wild.

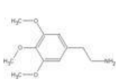
The top of the cactus above ground, also referred to as the crown, consists of disc-shaped buttons that are cut from the roots and dried. When done properly the top of the root will callous over and new buttons will eventually grow. When poor harvesting technique is used, however, the root is damaged and the entire plant dies. These buttons are generally chewed, or boiled in water to produce a psychoactive tea. The resulting infusion is extremely bitter and, in most cases, the user experiences some degree of nausea before the onset of the psychedelic effects. This is considered quite normal according to experienced users and historians.

Medicinal effects

The effective dose for mescaline is about 300 to 500 mg (equivalent to roughly 5 grams of dried peyote) and the effects last about 10 to 12 hours. When combined with appropriate set and setting, peyote is reported to trigger states of deep introspection and insight that have been described as being of a metaphysical or spiritual nature. At times, these can be accompanied by rich visual or auditory effects (see synesthesia). Unless one is embarking on the experience in a ceremonial context conducted by a "Peyotero" with much experience, similar to a shaman or medicine man, it is recommended, for safety reasons, that the user be accompanied at all times by someone who is not likewise intoxicated. This person is referred to by some as a "guide" or "trip sitter". In spite of this, a person who wants to undergo such an experience must observe two points to guarantee a mentally healthy trip: set and setting, i.e., the state of mind and the situation one is living at the session. The works of Timothy Leary explain this further.

History

From earliest recorded time, peyote has been used by indigenous peoples, such as the Huichol peoples of northern Mexico and the Navajo in the southwestern United States, as a part of traditional religious rites. In the late 1800s, the tradition began to spread northward as part of a revival of native spirituality under the auspices of what came to be known as the Native American Church, whose members refer to peyote as "the medicine", and use it to combat alcoholism and other social ills. The Native American Church is one among several religious organizations that use peyote as part of their religious practice.


chemical structure of mescaline

A resurgence of interest in the use of peyote was spawned in the 1970s by accounts of its use in the early works of writer Carlos Castaneda. Don Juan Matus, the pseudonym for Castaneda's instructor in the use of peyote, used the name "Mescalito" to refer to an entity that purportedly can be sensed by those using peyote to gain insight in how to live one's life. Later works of Castaneda asserted that the use of such psychotropic substances was not necessary to achieve heightened awareness and de-emphasized the use of peyote as a

general means to achieve this end. Castaneda's writing has been largely discredited as serious anthropological research and is generally considered to be allegorical fiction.

Legality

USA

United States federal law (and many state laws) protect the harvest, possession and consumption (but not cultivation) of peyote as part of "bonafide religious ceremonies" (the federal regulation is 42 USC §1996a, "Traditional Indian religious use of the peyote sacrament," exempting only Native American use, while most state laws exempt any general "bonafide religious activity"). These laws notwithstanding, religious or therapeutic use not under the aegis of the Native American Church has often been targeted by local law enforcement agencies, and non-natives attempting to establish spiritual centers based on the consumption of peyote as a sacrament or as medicine, such as the Peyote Foundation in Arizona, have been prosecuted.

Canada

Under the Canadian Controlled Drugs and Substances Act mescaline is defined as illegal but peyote is specifically exempt. [Controlled Drugs And Substances Act] "17. Mescaline (3,4,5–trimethoxybenzeneethanamine) and any salt thereof, but not peyote (lophophora)"

International

Article 32 of the Convention on Psychotropic Substances allows nations to exempt certain traditional uses of peyote from prohibition:

> A State on whose territory there are plants growing wild which contain psychotropic substances from among those in Schedule I and which are traditionally used by certain small, clearly determined groups in magical or religious rites, may, at the time of signature, ratification or accession, make reservations concerning these plants, in respect of the provisions of article 7, except for the provisions relating to international trade.

See also

- Entheogen
- Mescaline

Psychedelic mushroom

Psychedelic mushrooms are fungi that contain psychedelic substances, such as psilocybin, psilocin, or muscimol. The most common colloquial terms for psychedelic mushrooms are *magic mushrooms*, *boomers*,[1] or just '*shrooms*, though there are many more.

Categorization

Psychedelic mushrooms can be divided into two groups: the psilocybin-bearing mushrooms, found primarily in the Psilocybe genus, and the muscimol-containing mushroom Amanita muscaria.

Psilocybe mushrooms contain psilocybin and/or psilocin, psychedelic tryptamines that are structurally similar to serotonin, a strong regulator of mood, state of mind, and consciousness. Several species of Psilocybe also contain the alkaloid baeocystin, which is a demethylated derivative of psilocybin. Other genera that contain psilocybin include Conocybe, Copelandia, Gymnopilus, Inocybe and Panaeolus.

Amanita muscaria, or Fly Agaric, contains many entheogenic elements, most notably muscimol, but also including muscazone, ibotenic acid and muscarine. It produces a much different experience compared to a Psilocybe mushroom. This mushroom is toxic in large doses, as ibotenic acid and muscazone can cause unpleasant side-effects such as nausea or even permanent damage, although there are very few fatalities caused by Amanita muscaria. Recreational users who wish to consume the Amanita muscaria often heat dry or cook the mushrooms, as the high temperature is believed to reduce negative effects by converting ibotenic acid into muscimol.

History

Various cultures throughout the ages have used psychedelic fungi for shamanistic and other purposes; rock paintings in the Sahara of mushroom effigies date back to 7000 BCE.

Mesoamerican mushroom stones of the pre-classic Mayans representing deified mushrooms date back to approximately 500 BCE, Psilocybin mushrooms were a revered tradition in native Central American cultures at the time of the European invasion, and have been in continuous use up to the present. Named teonanácatl ("flesh of the gods") in Nahuatl, they may have been employed for healing, divination and for intercession with spirits. Since the beginning of the Latin American colonial era, their use has been hidden due to persecution by the Christian church, which branded all native religious practices, especially those employing entheogenic sacraments, as "pagan".

Some scholars believe that Soma, the drink mentioned in Vedic literature, was derived from psychedelic mushrooms; R. Gordon Wasson suggests that this was amanita muscaria, which is known to have been used in Siberian shamanism. That Nordic Vikings may have used fly-agaric to produce their berserker rages was first suggested by the Swedish professor Samual Ödman in 1784. Ödman based his theory on reports about the use of fly-agaric among Siberian shamans. The notion has become widespread since the 19th century, but no contemporary sources mention this use or anything similar in their description of berserkers. Today, it is generally considered an unproven speculation.

According to the BBC, the first documented use of psychedelic mushrooms was in the Medical and Physical Journal: In 1799, a man who had been picking mushrooms for breakfast in London's Green Park included them in his harvest, accidentally sending his entire family on a trip. The doctor who treated them later described how the youngest child "was attacked with fits of immoderate laughter, nor could the threats of his father or mother refrain him."

In 1957, amateur mycologist R. Gordon Wasson published an article for Life describing his experiences with psilocybin mushrooms while a guest in the rituals of the Mazatec shaman Maria Sabina in a mountain village in the Mexican state of Oaxaca. His account triggered a wave of experimentation with these mushrooms which resulted in their eventual classification in the United States as a Schedule I drug under the Controlled Substances Act.

The introduction of westerners into the previously secret rites was later rued by Maria Sabina: "From the moment the foreigners arrived, the 'holy children' (a Mazatec euphemism for the mushrooms, which are otherwise not named directly) lost their purity. They lost their force, they ruined them. Henceforth they will no longer work. There is no remedy for it."

Effects

As with many psychoactive substances, the effects of any mushrooms consumed are subjective and unpredictable. Generally speaking, the experience of psilocybin containing mushrooms lasts four to six hours or more. The effect is typically inwardly oriented, with strong visual and auditory components. Visions and revelations may be experienced, and the effect can range from exhilarating to distraught. There can be also a total absence of effects, even with large doses.

The effects of mushrooms are strongly dependent upon set and setting. The Mazatecs purify themselves before a velada (or "vision quest") by abstaining from meat, eggs, alcohol and sex for four days. The veladas are always done in the dark, in a protected and sealed space which no one may enter or leave until all have regained their composure. Modern psychonauts often speak of "packing for the trip", by which is meant a loading of information into the brain prior to "departure", for example, by reading a philosophical writing or watching natural history or science documentaries in the days immediately prior to a planned experience. Experienced users find that there are ways of adjusting their environment to enhance their trip.

There have been calls for medical investigation of the use of psilocybin-containing mushrooms for the treatment of chronic cluster headaches, following numerous anecdotal reports of benefits.[2]

Physical

Physical effects are all related to how many mushrooms are consumed. Low doses exhibit effects along the lines of feelings of relaxation or peace, a feeling of heaviness or lightness, and loss of appetite.[3] Higher doses cause numerous effects like a feeling of coldness in some users, numbness of the mouth and adjacent features, nausea, weakness in the limbs (making locomotion difficult), excessive yawning which usually occurs during the come-up, swollen features, pupil dilation, and stiffness in points of the body, often the result of the users staying in awkward positions because of their inability to accurately judge the flow of time and their level of fatigue.

Sensory

As with many hallucinogens, the sensory effects are often the most dramatic of the experience. Most general doses cause a noticeable enhancement and contrasting of worldly colors, surfaces that seem to ripple, shimmer, or breathe, and some visual hallucinations.[1] Heavy experiences cause complex open and closed eye visuals, objects that warp, morph, or change solid colors (juxtaposed with the free-flowing and changing colors of LSD), a sense of melding into the environment, trails, and auditory hallucinations. Natural and artificial sounds seem to be heard with increased clarity; music, for example, can often take on a profound sense of cadence and depth. Intriguingly, some users speak about the feeling of their senses overlapping or synesthesia, a rather interesting experience wherein it causes, for example, a visualization of color upon hearing a particular sound. Unusual natural designs, such as wood grain, seem to flow like rivers and finer details are noticed more sharply. Interesting textures can be quite stimulating to some users.

Emotional

Feelings of euphoric bliss, relaxation, peace, wonder, anxiety, or fear have all been reported.[4] A childlike sense of intrigue about the world on common doses is contrasted with cosmic revelations and perceptions of a "higher power" on large amounts. Some users may experience intense episodes of hilarity, such as laughing for the duration of the psychedelic experience.[1] Emotions can be experienced with increased sensitivity. Heavier trips carry the increased possibility of a surreal event known as ego death, whereby the user loses the sense of boundaries between their self and the environment, creating a sort of perceived universal unity. Also, anxiety and paranoia are possible and if they become severe enough they could culminate into a bad trip. However, this can be easily offset by being in a comfortable place.

Psychological

Mushrooms cause the mind to conduct itself in an unusual manner. Abstract thoughts develop and are often difficult to explain to others correctly. An intricate thought pattern becomes apparent, climaxing in deep philosophical or introspective silence. Complex personal issues may be taken on full force by more experienced users, helping them arrive at a conclusion and make an appropriate change to their lifestyle. During this process, a user may also gain a new perspective on a thought they've held for years. The mind seems to flow more lucidly from idea to idea, making such things as improvisation easier. The natural filters of the mind are bypassed, causing a large increase in mental stimulation and creativity. Time dilation has been reported, with minutes and seconds taking an unusually large amount of time to pass. There may also be some indecisiveness in deciding what to do or get. Some people find that they experience stimulation of the verbal faculties (such as speech and singing), a phenomenon known as glossolalia, experimenting with phonetics like vowels, consonants, or click consonants

Dosage

Dosage of psilocybin mushrooms depends on the total psilocybin and psilocin content of the mushrooms, which varies significantly both between species and within the same species, but is typically around 0.5-2% of the dried weight of the mushroom. A typical dose of the rather common species, Psilocybe cubensis, is approximately 1 to 3 grams, corresponding with 10 to 30 milligrams psilocybin and psilocin, while about 3 to 5 grams dried material or 30 to 50 milligrams of psilocybin/psilocin is considered a heavy dose. Mushrooms are approximately 90% water, though dosages for fresh mushrooms are not 10 times higher as some of the psilocybin and much of the psilocin are lost from oxidation in the drying process.

Legal status

In many countries, psilocybin and psilocin containing mushrooms are illegal. This is because these substances are controlled by the UN convention on psychotropic substances of 1971. The mushrooms themselves are not listed as a controlled substance. Nonetheless, there is an active international trade both in mushrooms and in spores, which can be grown in sterile medium. Fly Agaric is not a controlled substance in most countries. The new drugs act of 2005 has been changed so that now "magic mushrooms" are a class A drug. Possession can get you a seven year sentence and/or an unlimited fine. Supplying or dealing can get you life in jail and an unlimited fine.

The Netherlands

In the Netherlands, magic mushrooms can be obtained in "smart shops" which specialise in ethnobotanicals. Magic mushrooms, whether dried or fresh were legal until 2001, when the Supreme Court of The Netherlands ruled dry mushrooms to be an illegal preparation of psilocybin and psilocin. The limitation to fresh mushrooms (which go bad quite fast) is severely reducing the export of magic mushrooms. In a series of court cases during 2003-2005 this was challenged by De Sjamaan, a Dutch mushroom wholesaler. The vice president of the International Narcotics Control Board (INCB) of the UN testified to the court that the UN does not see dried or prepared psilocybe mushrooms as a controlled substance. Explanation: Psilocybe mushrooms are not listed as controlled substances, therefore preparations are also not controlled. Preparations of the controlled substances psilocybin and psilocin (i.e. tablets, etc) are controlled. Various mushroom experts have testified that there is no way to see the difference between passively and actively dried mushrooms. The court decided to agree to other viewpoints of De Sjamaan in order not to touch the subject of the UN's stance. The court also decided not to publish the testimony of the vice president of the INCB. The high court ruled that:

- there is no definition in regards to water content, which differentiates between a dry mushroom and a fresh mushroom. - passively dried mushrooms (natural desiccation) are legal. - a police-officer is not skilled to differentiate between a fresh and dry mushroom.

Canada

Mushroom spore kits are legal and are sold openly in stores as the spores themselves are not illegal. However, production, sale and possession of psilocybin mushrooms is illegal.

Japan

Before 2002, psilocybin mushrooms were widely available in Japan, often sold in mail-order shop, online vendor and "smart shops" similar to those of the Netherlands. In June 2002, Japan Health, Labor and Welfare Ministry added psilocybin mushrooms to Schedule Narcotics (similar to U.S. Schedule I of Controlled Substances Act) of Narcotic and Psychotropic Drug Control Law (similar to U.S. Controlled Substances Act). Use, production, trafficking, growing, possession, botanizing of psilocybin mushrooms is now illegal in Japan. However, muscimol-containing mushrooms such as Amanita muscaria are still not controlled in Japan, probably due to its notorious difficulty in obtaining a psychedelic experience.

New Zealand

In New Zealand, psilocybin mushrooms are class A drugs, putting them in the highest class of illicit compounds along with heroin and LSD. They do not have to be prepared in any way for possession to be illegal.

Republic of Ireland

Until 31 January, 2006, unprepared psilocybin mushrooms were legal in the Republic of Ireland. On that date they were made illegal by a ministerial order. This decision was partly based on the death of well-known Dubliner Colm Hodkinson, age 33, at a Halloween party on 30th October 2005, who died after jumping off of a balcony after consuming legally purchased magic mushrooms.[5]

United Kingdom

As of 18 July 2005, both dried and "prepared" (that is, made into a tea) psilocybin mushrooms were made illegal in the United Kingdom. Prior to this date, fresh mushrooms were widely available (even in city centre shops), but Clause 21 of the Drugs Bill 2005 made fresh psychedelic mushrooms ("fungi containing psilocin"), a Class A drug. However, mushrooms spores are not illegal, due to the fact they do not carry psilocin until they are cultivated.

United States of America

In the United States, possession of psilocybin-containing mushrooms is illegal because they contain the Schedule I drugs psilocin and psilocybin. Spores, however, which do not contain psychoactive chemicals, are only explicitly illegal in California, Idaho, and Georgia. In the state of Florida, fresh or unprepared psilocybin mushrooms that grow wild are legal to possess.

In all states, except possibly New Mexico, growing psilocybin-containing mushrooms from spores is considered manufacture of a controlled substance. In New Mexico, on June 15, 2005, the New Mexico appeals court ruled that growing psilocybin mushrooms for personal use is not manufacture of a controlled substance.[6]

Drug trade

Production

It is not difficult to cultivate Psilocybe mushrooms (esp. Psilocybe cubensis). The legal availability of spores and mycelium varies by country and state. Most of the other supplies needed for mushroom cultivation (mason jars, potting supplements, rye, brown rice flour) are easily obtained. One can also purchase kits through the mail or Internet that include everything one needs for personal growing. These grow kits are often used by amateur growers, with varying rates of success and yields; contamination of the supplies is a common problem.

Trafficking

Because mushrooms can be grown indoors (namely Psilocybe cubensis and Panaeolus cyanescens), they are generally grown within the same national borders as they are sold. There have been few high-profile cases of mushroom producers and traffickers being caught or prosecuted.

While mushrooms may be distributed by organized crime, more often they are moved by informal affiliations of acquaintances and fellow users, and do not often travel long distances. They are sold in plastic bags containing either whole dried or powdered, sometimes crushed, fungi, and are generally sold by weight. They are sometimes incorporated into chocolate or baked into brownies, cakes, or muffins. The typical price for an ounce of dried mushrooms can range from as little as 70$ to 400$ depending on the quality of the product, as well as their availability in the area. The quality of the product is generally about the same, varying only as can be expected with a non-synthetic psychedelics. The major factor in the quality of this drug is how well they have been stored, with well dried whole mushrooms kept in cool dark places being ideal. Contaminated grows yield poor quality, possibly toxic mushrooms. One should be extremely cautious of any mushrooms which have unusual growths or mold, as well as any mushrooms which may have been harvested from the same grow as mushrooms with these growths.

The potency of mushrooms can vary greatly depending on the growing conditions, and buyers of this and any other drug run the risk of ingesting a poisonous, mis-identified species, or being cheated by substitutions or cutting of the mushrooms with other, non-psychedelic varieties, or by non-psychedelic varieties laced with other psychedelics, most often LSD.

Identification

While growing psychedelic mushrooms in a controlled environment is generally considered easier and safer than searching for them in the wild, such mushrooms can be found in places like farms, parks, and stables.

Amanita muscaria

Amanita muscaria can be easily confused by the layperson with Amanita pantherina as well as other toxic Amanitas. Misidentified Amanitas are the cause of 95% of fatal mushroom poisonings. For this reason, extreme caution should be used when attempting to identify an Amanita muscaria for ingestion.

Recreational use of these mushrooms is limited in spite of the fact that they are legal to buy/sell in most areas. Most users only eat the mushrooms once or twice due to their unpleasant side effects and the tendency for a recreational user to try too much causing very harsh side effects. Light doses (1 – 3 grams dried) are described to be similar to alcohol and a very 'social buzz'. Higher doses (9+ grams dried) have been described as having the flu along with delirium usually accompanied with vomiting and stomach discomfort.

See also

- Ergot, another form of psychoactive fungus

Notes

1. ^ ***a*** ***b*** c Cynthia Kuhn, Scott Swartzwelder, and Wilkie Wilson. Hallucinogens (pg. 83) from Buzzed: The Straight Facts about the Most Used and Abused Drugs from Alcohol to Ecstasy (W.W. Norton & Company Inc., 1998 & 2003). ISBN 0-393-32493-1.
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Soma

Soma (Sanskrit), or *Haoma* (Avestan), from Proto-Indo-Iranian *sauma-, was a ritual drink of importance among the early Indo-Iranians, and the later Vedic and greater Persian cultures. It is frequently mentioned in the Rigveda, which contains many hymns praising its energizing or intoxicating qualities. In the Avesta, Haoma has an entire Yasht dedicated to it.

It is described as prepared by pressing juice from the stalks of a certain mountain plant, which has been variously hypothesized to be a psychedelic mushroom, cannabis, peganum harmala, or ephedra. In both Vedic and Zoroastrian tradition, the drink is identified with the plant, and also personified as a divinity, the three forming a religious or mythological unity.

Etymology

Both Soma and the Avestan Haoma are derived from Proto-Indo-Iranian *sauma-. The name of the Scythian tribe Hauma-varga is related to the word, and probably connected with the ritual. The word is derived from an Indo-Iranian root *sav- (Sanskrit sav-) "to press", i.e. *sav-ma- is the drink prepared by pressing the stalks of a plant (cf. es-presso). The root is probably Proto-Indo-European (*sewh-), and also appears in son (from *suhnu-, "pressed out" i.e. "newly born").

Vedic Soma

In the Vedas, Soma is portrayed as sacred and as a god (deva). The god, the drink and the plant probably referred to the same entity, or at least the differentiation was ambiguous. In this aspect, Soma is similar to the Greek ambrosia (cognate to amrita); it is what the gods drink, and what made them deities. Indra and Agni are portrayed as consuming Soma in copious quantities. In vedic mythology, the eagle Aquila brought soma to Indra during her battle with the serpent Hydra. The consumption of Soma by human beings was probably under the belief that it bestowed divine qualities on them.

In the Rigveda

The Rigveda (8.48.3, tr. Griffith) states,

a ápma sómam amUt abhkmâganma jyótir ávidma devân c kíC nknám asmân k[Gavad árti% kím u dhkrtír am[ta mártyasya We have drunk Soma and become immortal; we have attained the light, the Gods discovered. Now what may foeman's malice do to harm us? What, O Immortal, mortal man's deception?

The Ninth Mandala of the Rigveda is known as the *Soma Mandala*. It consists entirely of hymns addressed to *Soma Pavamana* ("purified Soma"). The drink Soma was kept and distributed by the Gandharvas. The Rigveda associates the Sushoma, Arjikiya and other regions with Soma (e.g. 8.7.29; 8.64.10-11). Sharyanavat was possibly the name of a pond or lake on the banks of which Soma could be found.

The plant is described as growing in the mountains (giristha, cf. Orestes), with long stalks, and of yellow or tawny (hari) colour. The drink is prepared by priests pounding the stalks with stones, an occupation that creates tapas (literally "heat", later referring to "spiritual excitement" in particular). The juice so gathered is mixed with other ingredients (including milk and honey) before it is drunk.

Growing far away, in the mountains, Soma had to be purchased from travelling traders. The plant supposedly grew in the Hindukush and thus it had to be imported to the Punjab region. Later, knowledge of the plant was lost altogether, and Indian ritual reflects this, in expiatory prayers apologizing to the gods for the use of a substitute plant (e.g. rhubarb) because Soma had become unavailable.

In Hinduism

In Hindu art, the god Soma was depicted as a bull or bird, and sometimes as an embryo, but rarely as an adult human. In Hinduism, the god Soma evolved into a lunar deity, and became associated with the underworld. The moon is the cup from which the gods drink Soma, and so Soma became identified with the moon god Chandra. A waxing moon meant Soma was recreating himself, ready to be drunk again. Alternatively, Soma's twenty-seven wives were daughters of Daksha, who felt he paid too much attention to just one of his wives,

Rohini. He cursed him to wither and die, but the wives intervened and the death became periodic and temporary, and is symbolized by the waxing and waning of the moon.

The famous ayurvedic scholar Susruta wrote that the best Soma is found in the upper Indus and Kashmir region (Susruta Samhita: 537-538, SS.CS. 29.28-31).

Avestan Haoma

The continuing importance of Haoma in Zoroastrianism may be glimpsed from the Avesta (particularly in the HMm Yast, Yasna 9.11), and Avestan language *hauma also survived as middle Persian hMm. The plant Haoma yielded the essential ingredient for the ritual drink, parahaoma.

In the HMm yašt of the Avesta, the Yazata (divine) Haoma appears to Zoroaster "at the time of pressing" (havani ratu) in the form of a beautiful man. Yasna 9.1 and 9.2 exhort him to gather and press Haoma plants. Haoma's epitheta include "the Golden-Green One" (zairi-, Sanskrit hari-), "righteous" (ašavan-), "furthering righteousness" (aša-vazah-), and "of good wisdom" (hu.xratu-, Sanskrit sukratu-).

In Yasna 9.22, Haoma grants "speed and strength to warriors, excellent and righteous sons to those giving birth, spiritual power and knowledge to those who apply themselves to the study of the nasks". As the religion's chief cult divinity he came to be perceived as its divine priest. In Yasna 9.26, Ahura Mazda is said to have invested him with the sacred girdle, and in Yasna 10.89, to have installed Haoma as the "swiftly sacrificing zaotar" (Sanskrit hotar) for himself and the Amesha Spenta. Haoma services were celebrated until the 1960s in a strongly conservative village near Yazd.

Candidates for the Soma plant

There has been much speculation as to the original Proto-Indo-Iranian Sauma plant. It was generally assumed to be hallucinogenic, based on RV 8.48 cited above. But note that this is the only evidence of hallucinogenic properties, in a book full of hymns to Soma. The typical description of Soma is associated with excitation and tapas. Soma is associated with the warrior-god Indra, and appears to have been drunk before battle. For these reasons, there are energizing plants as well as hallucinogenic plants among the candidates that have been suggested. Including the mushroom amanita muscaria, which was widely used as a brew of sorts among Siberian shamans for its hallucinogenic and 'religious experience' inducing properties. In fact, several texts like the Atharva Veda extol the medicinal properties of Soma and he is regarded as the king of medicinal herbs (and also of the Brahmana class).

Since the late 1700s, when Anquetil-Duperron and others made portions of the Avesta available to western scholarship, several scholars have sought a representative botanical equivalent of the haoma as described in the texts and as used in living Zoroastrian practice. Most of the proposals concentrated on either linguistic evidence or comparative pharmacology or reflected ritual use. Rarely were all three considered together, which usually resulted in such proposals being quickly rejected.

In the late 19th century, the highly conservative Zoroastrians of Yazd (Iran) were found to use Ephedra (genus Ephedra), which was locally known as hum or homa and which they exported to the Indian Zoroastrians. (Aitchison, 1888) The plant, as Falk also established,

requires a cool and dry climate, i.e. it does not grow in India (which is either too hot or too humid or both) but thrives in central Asia. Later, it was discovered that a number of Iranian languages and Persian dialects have hom or similar terms as the local name for some variant of Ephedra. Considered together, the linguistic and ritual evidence appeared to conclusively establish that haoma was some variant of Ephedra.

In Western Culture

- Soma is mentioned in the well-known Christian hymn "Dear Lord and Father of Mankind", by the American Quaker poet, John Whittier (1807-1892) who saw the drinking of soma as causing a distraction of the mind from the proper worship of God. Verse four of the original is usually omitted, but includes the phrase, "In sensual transports - wild as vain, we brew in many a Christian fane the heathen soma still..."
- In Aldous Huxley's dystopian novel Brave New World, Soma is a popular hallucinogenic drug which is sometimes used in a pseudo-religious capacity.
- In Blake's 7, Soma is used as a tranquiliser and sedative. Frequently imbibed as a green liquid, Soma is used as a social drug almost like alcohol.

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Herbal and fungal stimulants

Coca | Cocoa | Coffea | Ephedra | Khat | **Nicotiana rustica** | Tea | Tobacco | Yerba mate

Coca

Scientific classification

Kingdom: Plantae
Division: Magnoliophyta
Class: Magnoliopsida
Order: Malpighiales
Family: Erythroxylaceae
Genus: Erythroxylum
Species: *E. coca*
Binomial name *Erythroxylum coca*

Coca is a plant in the family Erythroxylaceae, native to northwestern South America. The plant plays a significant role in traditional Andean culture, but is best-known in modern times for the stimulant drug cocaine that is extracted from its new fresh leaf tips in a similar fashion to tea bush harvesting.

The plant resembles a blackthorn bush, and grows to a height of 2-3 m (7-10 ft). The branches are straight, and the leaves, which have a green tint, are thin, opaque, oval, more or less tapering at the extremities. A marked characteristic of the leaf is an areolated portion bounded by two longitudinal curved lines, one line on each side of the midrib, and more conspicuous on the under face of the leaf.

The flowers are small, and disposed in little clusters on short stalks; the corolla is composed of five yellowish-white petals, the anthers are heart-shaped, and the pistil consists of three carpels united to form a three-chambered ovary. The flowers mature into red berries.

The leaves are sometimes eaten by the maggots of the moth Eloria noyesi.

Species and classification

There are twelve main species and varieties (Erythroxylum coca). Two subspecies, E. coca var. coca and E. coca var. ipadu, are almost indistinguishable phenotypically; a related high cocaine-bearing species has two subspecies, E. novogranatense var. novogranatense and E. novogranatense var. truxillense that are phenotypically similar, but morphologically distinguishable. Under the older Cronquist system of classifying flowering plants, this was placed in an order Linales; more modern systems place it in the order Malpighiales.

Cultivation and uses

Coca is traditionally cultivated in the lower altitudes of the eastern slopes of the Andes, or the highlands depending on the species grown. Since ancient times, its leaves have been used as a stimulant by some of the indigenous people of Venezuela, Colombia, Ecuador, Peru, Bolivia, Brazil, northern Argentina, and Trinidad. In the highlands, it is used as a breathing aid. It also has religious and symbolic significance. Since the 1980s, the cultivation of coca has become controversial because it is used for the manufacture of the drug cocaine, which is illegal in most countries for recreational use, but legal for medical uses, e.g., nose and throat anaesthesia.

Good fresh samples of the dried leaves are uncurled, are of a deep green on the upper, and a grey-green on the lower surface, and have a strong tea-like odor; when chewed they produce a faint numbness in the mouth, and have a pleasant, pungent taste. They are traditionally chewed with lime to increase the release of cocaine from the leaf. Bad specimens, usually old or stale leaves, have a camphoraceous smell and a brownish colour, and lack the pungent taste.

The seeds are sown from December to January in small plots (almacigas) sheltered from the sun, and the young plants when at 40-60 cm in height are placed in final planting holes (aspi), or, if the ground is level, in furrows (uachos) in carefully weeded soil. The plants thrive best in hot, damp and humid situations, such as the clearings of forests; but the leaves most preferred are obtained in drier localities, on the sides of hills. The leaves are gathered from plants varying in age from one and a half to upwards of forty years, but only the new fresh growth is harvested. They are considered ready for plucking when they break on being bent. The first and most abundant harvest is in March, after the rains; the second is at the end of June, the third in October or November. The green leaves (matu) are spread in thin layers on coarse woollen cloths and dried in the sun; they are then packed in sacks, which must be kept dry in order to preserve the quality of the leaves.

Pharmacological aspects

The pharmacologically active ingredient of coca is the alkaloid cocaine which is found in the amount of about 0.2% in fresh leaves. Besides cocaine, the coca leaf contains a number of other alkaloids, including Methylecgonine cinnamate, Benzoylecgonine, Truxilline, Hydroxytropacocaine, Tropacocaine, Ecgonine, Cuscohygrine, Dihydrocuscohygrine, Nicotine and Hygrine. Some of these non-psychoactive chemicals are still used for the flavouring of Coca-Cola. When chewed, Coca acts as a stimulant to help suppress hunger sensations, thirst, and fatigue. Some anesthetics such as Novocaine are derived from the coca plant. The LD50 of coca extract is 3450 mg/kg, however, the LD50 of the extract based on its cocaine content is 31.4 mg/kg, indicating that the coca leaf contains constituents other than cocaine that may contribute to a toxic effect of the plant

Traditional uses

In the Andes, the indigenous peoples have been chewing the leaves of the coca plant for millennia. They traditionally carried a woven pouch called a chuspa or huallqui in which they kept a day's supply of coca leaves, along with a small amount of ilucta or uipta, which is made from pulverized unslaked lime or from the ashes of the quinoa plant. A tiny quantity of ilucta is chewed together with the coca leaves; it softens their astringent flavor and activates the alkaloids. Other names for this basifying substance are llipta in Peru and the Spanish word lejía, lye in English. Many of these materials are salty in flavor, but there are variations. The most common base in the La Paz area of Bolivia is a product known as lejía dulce (sweet lye) which is made from quinoa ashes mixed with anise and cane sugar, forming a soft black putty with a sweet and pleasing licorice flavor. In some places, baking soda is used under the name bico.

The practice of chewing coca was most likely originally a simple matter of survival. The coca leaf contained many essential nutrients in addition to its more well-known mood-altering alkaloid. It is rich in protein and vitamins, and it grows in regions where other food sources are scarce. The perceived boost in energy and strength provided by the cocaine in coca leaves was also very functional in an area where oxygen is scarce and extensive walking is essential. This was also used to fool the feeling of hunger, sleepiness and head-aches linked to altitude and other altitude sicknesses. The coca plant was so central to the worldview of the Yunga and Aymara tribes of South America that distance was often measured in units called "cocada", which signified the number of mouthfuls of coca that one would chew while walking from one point to another. Cocada can also be used as a measurement of time, meaning the amount of time it takes for a mouthful of coca to lose its flavor and activity. In testament of the significance of coca to indigenous cultures, it is widely believed that the word "coca" probably originally meant "plant."

Coca was also a vital part of the religious cosmology of the Andean tribes in the pre-Inca period as well as throughout the Inca Empire (Tahuantinsuyu). Coca was historically employed as an offering to the Sun, or to produce smoke at the great sacrifices; and the priests, it was believed, must chew it during the performance of religious ceremonies, otherwise the gods would not be appeased. Coca is still held in veneration among the indigenous and mestizo peoples of Peru, Bolivia, Ecuador, Colombia and northern Argentina and Chile. It is believed by the miners of Cerro de Pasco to soften the veins of ore, if masticated (chewed) and thrown upon them (see also Cocomama). Coca leaves play a crucial part in offerings to the apus (mountains), Inti (the sun), or Pachamama (the earth). Coca leaves are often read in a form of divination analogous to reading tea leaves in other cultures.

In the Sierra Nevada de Santa Marta, on the Caribbean Coast of Colombia, coca is consumed by the Kogi, Arhuaco & Wiwa by using a special gadget called poporo. The poporo is the mark of manhood, but it is a female's sexual symbol. It represents the womb and the stick is a phallic symbol. The movements of the stick in the poporo symbolize the sexual act. For a man the poporo is a good companion which means "food" "woman", "memory" and "meditation". Women are prohibited from using coca. It is important to stress that poporo is the symbol of manhood. But it is the woman who gives men their manhood. When the boy is

ready to be married, his mother will initiate him in the use of the coca. This act of initiation is carefully supervised by the mama, a traditional leader.

The activity of chewing coca is called mambear, chacchar or acullicar, borrowed from Quechua, or in Bolivia, picchar, derived from the Aymara language. The Spanish masticar is also frequently used. Doing so usually causes users to feel a tingling and numbing sensation in their mouths, similar to receiving Novocaine during a dental procedure. Even today, chewing coca leaves is a common sight in indigenous communities across the central Andean region, particularly in places like the mountains of Bolivia, where the cultivation and consumption of coca is as much a part of the national culture similar to chicha, like wine is to France or beer is to Germany. It also serves as a powerful symbol of indigenous cultural and religious identity, amongst a diversity of indigenous nations throughout South America. Bags of coca leaves are sold in local markets and by street vendors. Commercially manufactured coca teas are also available in most stores and supermarkets, including upscale suburban supermarkets.

Mate de coca, sometimes called "coca tea", is a tisane made from the leaves of the Coca plant (Eritroxilécea). The consumption of coca tea is a common occurrence in many South American countries. Coca tea is also used for medicinal and religious purposes by many indigenous tribes in the Andes. On the "Inca Trail" to Macchu Picchu, guides also serve coca tea with every meal because it is widely believed that it alleviates the symptoms of mild altitude sickness. And traditionally, official governmental persons travelling to La Paz in Bolivia are greeted by a mate de coca. News reports noted that Princess Anne and the late Pope John Paul II drank the beverage during visits to the region.

International use

Coca has a long history of export and use around the world—legal and illegal. Modern export of processed coca (as cocaine) to global markets is well documented, and coca leaves are exported for coca tea, flavoring (Coca-Cola), and for medical use. Several pipes taken from Shakespeare's residence and dated to the seventeenth century have shown evidence of cocaine, Queen Victoria of England was also a cocaine user; the drug was first introduced to Europe in the 16th century.

Industrial use

Coca is used industrially in the cosmetics and food industries. The Coca-Cola Company used to buy 115 tons of coca leaf from Peru and 105 tons from Bolivia per year, which it has used as a flavouring ingredient in its Coca-Cola formula. Coca is sold to the pharmaceutical industry where it is used for various anaesthetics. Coca is used to produce Coca Tea by Enaco S.A. (National Company of the Coca) a government enterprise in Peru. In Colombia, the Paeces, a Tierradentro (Cauca) indigenous community, started in December 2005 to produce a drink called "Coca Sek." The production method belongs to the resguardos of Calderas (Inzá) and takes about 150 kg of coca per 3000 produced bottles.

Legality

International

Article 26 of the Single Convention on Narcotic Drugs states:

1. If a Party permits the cultivation of the coca bush, it shall apply thereto and to coca leaves the system of controls as provided in article 23 respecting the control of the opium poppy, but as regards paragraph 2 (d) of that article, the requirements imposed on the Agency therein referred to shall be only to take physical possession of the crops as soon as possible after the end of the harvest. 2. The Parties shall so far as possible enforce the uprooting of all coca bushes which grow wild. They shall destroy the coca bushes if illegally cultivated.

The Article 23 controls referred to in paragraph 1 are rules requiring opium-, coca-, and cannabis-cultivating nations to designate an agency to regulate said cultivation and take physical possession of the crops as soon as possible after harvest. Article 27 states that "The Parties may permit the use of coca leaves for the preparation of a flavouring agent, which shall not contain any alkaloids, and, to the extent necessary for such use, may permit the production, import, export, trade in and possession of such leaves". This provision is designed to accommodate Coca-Cola and other producers of coca products.

In Bolivia, the president Evo Morales (elected in December, 2005), a former coca growers union leader, has promised to legalize the cultivation and traditional use of coca. Morales asserts that "coca no es cocaína"--the coca leaf is not cocaine. During his speech on 19 September 2006, he held a coca leaf in his hand to demonstrate its innocuity.[3]

In Peru, private companies already manufacture coca leaf products.

More recently, coca has been reintroduced to the U.S. as a flavoring agent in the herbal liquer Agwa.

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Cocoa

Cocoa is the dried and partially fermented fatty seed of the cacao tree from which chocolate is made. In the United States, 'cocoa' often refers to cocoa powder, the dry powder made by grinding cocoa seeds and removing the cocoa butter from the dark, bitter cocoa solids. Cocoa powder has an extremely bitter flavor.

A cocoa pod has a rough leathery rind about 3 cm thick (this varies with the origin of pod). It is filled with sweet, mucilaginous pulp called 'baba de cacao' in South America,

enclosing 30 to 50 large almond-like seeds (beans) that are fairly soft and pinkish or purplish in color.

History

The cacao tree apparently originated in the foothills of the Andes in the Amazon and Orinoco basins of South America. It was introduced into Central America by the ancient Mayas, and cultivated in Mexico by the Toltecs and later by the Aztecs.

Cocoa trees will grow in a very limited geographical zone, of approximately 10 degrees to the north and south of the Equator. Nearly 70% of the world crop is grown in West Africa.

Cocoa was an important commodity in Pre-Columbian Mesoamerica. Spanish chroniclers of the conquest of Mexico by Hernán Cortés relate that when Moctezuma II, emperor of the Aztecs, dined he took no other beverage than chocolate, served in a golden goblet and eaten with a golden spoon. Flavored with vanilla and spices, his chocolate was whipped into a froth that dissolved in the mouth. No less than 50 pitchers of it were prepared for the emperor each day, and 2000 more for nobles of his court.

Chocolate was introduced to Europe by the Spaniards and became a popular beverage by the mid 1500s. They also introduced the cacao tree into the West Indies and the Philippines. It was used in alchemical processes, where it was known as Black Bean.

The cacao plant was first given its name by Swedish natural scientist Carl von Linné (1707-1778), who called it "Theobroma cacao" or "food of the gods".

Production

World Production

Top Cocoa Producers - 2004 (million metric ton)

Côte d'Ivoire 1.33

Ghana 0.74

Indonesia 0.43

Nigeria 0.37

Brazil 0.17

Cambodia 0.13

Ecuador 0.09

World Total 3.6

Source: UN Food & Agriculture Organisation (FAO)[1]

About 3,000,000 tonnes of cocoa are grown each year. The global production was 1,556,484 t in 1974, 1,810,611 t in 1984, 2,672,173 t in 1994, 3,607,052 t in 2004 (record).

This is an increase of 131.7% in 30 years.

There are three varieties of the Theobroma cacao: Forastero, Criollo and Trinitario. The first comprises 95% of the world production of cacao, and is the most widely used. Overall, the highest quality of cacao comes from the Criollo variety and is considered a delicacy; however, Criollo is harder to produce, hence very few countries produce it, with the majority of production coming from Venezuela (Chuao and Porcelana). The Trinitario is a mix between Criollo and Forastero.

The Netherlands is the leading cocoa processing country, followed by the U.S..

Prices for cocoa reached a five-year high in November 2004 because exports from Côte d'Ivoire (Ivory Coast) were likely to decrease due to escalating violence in the region.

Cocoa and its products (including chocolate) are used world-wide. Belgium has the highest per-capita consumption at 5.5 kg, 10 times the world average [2].

Harvesting

When the pods ripen, they are harvested from the trunks and branches of the Cocoa tree with a curved knife on a long pole. The pod itself is green when ready to harvest, rather than red or orange. Normally, red or orange pods are considered of a lesser quality because their flavors and aromas are poorer; these are used for industrial chocolate. The pods are either opened on the field and the seeds extracted and carried to the fermentation area on the plantation, or the whole pods are taken to the fermentation area.

Processing

The harvested pods are opened with a machete, the pulp and cocoa seeds are removed and the rind is discarded. The pulp and seeds are then piled in heaps, placed in bins, or laid out on grates for several days. During this time, the seeds and pulp undergo "sweating", where the thick pulp liquifies as it ferments. The fermented pulp trickles away, leaving cocoa seeds behind to be collected. Sweating is important for the quality of the beans, which originally have a strong bitter taste. If sweating is overdone, the resulting cocoa may be ruined; if underdone the cocoa seed maintains a flavor similar to raw potatoes and becomes susceptible to mildew.

The liquified pulp is used by some cocoa producing countries to distill alcoholic spirits.

The fermented beans are dried by spreading them out over a large surface and constantly raking them. In large plantations, this is done on huge trays under the sun or by using artificial heat. Small plantations may dry their harvest on little trays or on cowhides. Finally, the beans are trodden and shuffled about (often using bare human feet) and sometimes, during this process, red clay mixed with water is sprinkled over the beans to obtain a finer color, polish, and protection against molds during shipment to factories in the United States,

the Netherlands, United Kingdom, and other countries. Drying in the sun is preferable to drying by artificial means, as no foreign flavours such as smoke or oil are introduced which might otherwise taint the flavour.

Chocolate production

To make 1 kg (2.2 pounds) of chocolate, about 300 to 600 beans are processed. In a factory, the beans are washed and roasted. Next they are de-hulled by a "nibber" machine that also removes the germ. The nibs are ground between three sets of stones into a thick creamy paste. This "liquor" is converted to cocoa powder by removing part of its fatty oils (the "cocoa butter") using a hydraulic press or the Broma process. This process produces around 50% cocoa butter and 50% cocoa powder. Standard cocoa powder has a fat content of approximately 10-12 percent. The extracted fatty oils are used in confectionery, soaps, and cosmetics.

Adding an alkali produces Dutch process cocoa powder, which is less acidic, darker and more mellow in flavour than what is generally available in most of the world. Regular (nonalkalized) cocoa is acidic, so when added to an alkaline ingredient like baking soda, the two react and leave a byproduct.

Uses of cocoa

The uses of cocoa beans are numerous. Chocolate or cocoa powder is mixed into cakes, ice creams, creams, cookies, or drinks as a natural flavour. It is the second most popular ice cream flavor, after vanilla. Sometimes it is merely used as a natural coloring agent for food, such as pasta.

One of the most common forms of cocoa is the chocolate or candy bar. It is also available in chocolate syrup, used as an ice cream topping or to make chocolate milk.

Cocoa has about twice as many antioxidants as does red wine, and up to three times more than green tea. Antioxidants are thought to be healthy compounds. Several chocolate manufacturers are beginning to offer chocolate products with guaranteed levels of these antioxidants, called polyphenols. The high antioxidant level in cocoa gives dark chocolate an ORAC value of 13,120 and milk chocolate an ORAC value of 6,740. [3] A 15-year study of elderly men published in the Archives of Internal Medicine in 2006 found a 50 percent reduction in cardiovascular mortality and a 47 percent reduction in all-cause mortality for the men regularly consuming the most cocoa, compared to those consuming the least cocoa from all sources.

Issues with cocoa as a commodity

- Sustainable cocoa farming encourages the economic, social and environmental conditions necessary to improve the livelihoods of small scale cocoa farmers in the tropics. The World Cocoa Foundationis working with private and public sector partners to support this effort.

- Many cocoa farmers receive a low price for their production. This has led to cocoa and chocolate being available as 'fair trade' items in some countries. However, this fair trade remains as a tiny percentage of the total trade.
- Child slavery has commonly been used in its production to cover the lower profit margin. According to the U.S. Department of State, more than 109,000 children were working on cocoa farms in Côte d'Ivoire in 'the worst forms of child labor' in 2002.[3] See Cocoa Protocol for an effort to end this practice.
- Pollination is exclusively by midges, which may be affected by pesticides.

Cocoa Trading

Cocoa beans, Cocoa butter and cocoa powder are traded on two world exchanges: London and New York. The London market is based on West African cocoa and New York on cocoa predominantly from South East Asia. Cocoa is the world's smallest soft commodity market. The futures price of cocoa butter and cocoa powder is determined by multiplying the bean price by a ratio. The combined butter and powder ratio has tended to be around 3.5. If the combined ratio falls below around 3.2, production ceases to be economically viable and some factories cease extraction of butter and powder and trade exclusively in cocoa liquor.

See also

- Caffeine

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Coffea

Scientific classification

Kingdom: Plantae
Division: Magnoliophyta
Class: Magnoliopsida
Order: Gentianales

Family: Rubiaceae
Genus: *Coffea*

Species

Coffea arabica - Arabica Coffee
Coffea benghalensis - Bengal coffee
Coffea canephora - Robusta coffee
Coffea congensis - Congo coffee
Coffea excelsa - Liberian coffee
Coffea gallienii
Coffea bonnieri
Coffea mogeneti
Coffea liberica - Liberian coffee
Coffea stenophylla - Sierra Leonian coffee

Coffea (*coffee*) is a genus of ten species of flowering plants in the family Rubiaceae. They are shrubs or small trees, native to subtropical Africa and southern Asia. Seeds of this plant are the source of a stimulating beverage called coffee. The seeds are called "beans" in the trade. Coffee beans are widely cultivated in tropical countries in plantations for both local consumption and export to temperate countries. Coffee ranks as one of the world's major commodity crops and is the major export product of some countries. In fact, coffee ranks second only to petroleum in terms of legally-traded products worldwide.

Botany

When grown in the tropics coffee is a vigorous bush or small tree easily grown to a height of 3–3.5 m (10–12 feet). It is capable of withstanding severe pruning. It cannot be grown where there is a winter frost. Bushes grow best at high elevations. To produce a maximum yield of coffee berries (800-1400 kg per hectare), the plants need substantial amounts of water and fertilizer. Calcium carbonate and other lime minerals is sometimes used to reduce acidity in the soil, which can occur due to run off of minerals from the soil in mountainous areas.**[1]**

There are several species of Coffea that may be grown for the beans, but Coffea arabica is considered to have the best quality. The other species (especially Coffea canephora (robusta)) are grown on land unsuitable for Coffea arabica. The tree produces red or purple fruits (drupes, or "coffee berries"), which contain two seeds (the "coffee beans", although not true beans). In about 5-10% of any crop of coffee cherries, the cherry will contain only a single bean, rather than the two usually found. This is called a 'peaberry' and contains a distinctly different flavor profile to the normal crop, with a higher concentration of the flavors, especially acidity, present due to the smaller sized bean. As such, it is usually removed from the yield and either sold separately (such as in New Guinea Peaberry), or discarded.

The coffee tree will grow fruits after 3–5 years, for about 50–60 years (although up to 100 years is possible). The blossom of the coffee tree is similar to jasmine in color and smell.

The fruit takes about nine months to ripen. Worldwide, an estimate of 15 billion coffee trees are growing on 100,000 km^2 of land.

Coffee is used as a food plant by the larvae of some Lepidoptera species including Dalcera abrasa, Turnip Moth and some members of the genus Endoclita including E. damor and E. malabaricus.

Processing

After picking, the coffee beans are pulped (usually using a mechanical pulper) to remove the bulk of the soft flesh, and then the beans are fermented (by one of several means, most often wet fermentation in water for 10 to 36 hours), then washed (to remove the last of the sticky mucilage not removed by fermentation) and dried (usually in the sun). This process is time-consuming, expensive and, for most growers, labour-intensive. Coffee at this stage is known as *milled beans*.

Once the raw ('green') coffee beans arrive in their destination country, they are roasted; this darkens their color and alters the internal chemistry of the beans and therefore their flavor and aroma. Blending can occur before or after roasting and is often performed to ensure a consistent flavor. Once the beans are roasted, they become much more perishable.

Problems of maintaining quality during bean production

Achieving consistently excellent milled beans is not easy. Problems include:

- Pests on the bushes (e.g., in Hawaii, scale insects and coconut mealy bugs)
- Poor pruning regimes (e.g., too many verticals that allow the bush to attempt too much and so produce inferior cherries)
- Poor fertiliser regimes (e.g., too little iron or insufficient nutriment for what are demanding plants)
- Bad picking (e.g., picking all the berries on a branch rather than those that are bright red, or picking the berries very late)
- Bad fermentation that produces unpleasant taints in the flavor
- Dilution of superior tasting beans with cheaper beans

The coffee bushes fruit aggressively when conditions permit, and the berries will develop at the expense of the rest of the bush. This consumes sugars in the leaves and can produce die-back (death of leaves and branches). Die-back can be severe and can damage not just the current year's production but the next year's production, which is borne on growth during the current year, leading into a two-year cycle of growth and production.

Commercial operators come under a variety of pressures to cut costs and maximise yield. Arguably the best flavours will be produced when the coffee is grown in organic conditions. Some people who grow organically do so primarily to obtain the premium prices organic beans command, an alternative strategy to increase profits.

The economics of growing coffee

It is very questionable whether small growers can generate a high return on capital growing coffee if they have less than 1.2 ha (3 acres or 12,000 m^2) and if they are based in the United States. The retail price of the beans varies between about 1 USD/pound for ripe berries to 9 USD/pound for extra fancy Kona milled beans, and there are many costs including fertiliser, irrigation, labour (e.g. picking and pruning) and land value. Integrated operations that capture much or all of the available revenue (by controlling the whole process from growing to retail) may generate higher returns.

It is estimated that 10 million people are working on plantations in the source lands of coffee. A single worker can harvest 50–100 kg of fruits per day, which results in 10–20 kg of raw coffee. Crops from Brazil (30%) and Colombia (10%) comprise 40% of the worldwide coffee production. As of 1998, the world's coffee production equals about 100 million sacks of coffee.

Many farmers receive a low price for their coffee because of a global market slump. This has led to coffee being available as a 'fair trade' labelled item in many countries.

Hand picked coffee

The highest quality coffee is generally hand picked. Normally, coffee growers harvest their coffee with portable vacuum packs, which the pickers wear on their backs and brush over the branches of the coffee bushes. Although it is much more efficient and quick to harvest the coffee with the vacuum packs, coffee beans do not become ripe at the same time, even if they are on the same tree, and thus many unripe beans are sucked away by the vacuum packs. Also, coffee pickers are sure to pick beans only of the highest quality. As a general rule, hand picked coffee is used for drip machines, while vacuum picked coffee is used to make instant coffee and decaffeinated coffee.

History

Coffee probably originated in the Kingdom of Kaffa (now part of the Southern Nations, Nationalities, and Peoples Region of Ethiopia), though there is controversy about its origins, with Yemen also suggested as an area of origin. One apocryphal tale claims that an Ethiopian goat-herder noticed his goats prancing about energetically, and found they were eating coffee berries, and tried some himself.

The crop first became popular in Arabia around the 13th century, and Islam's prohibition against alcoholic beverages probably enhanced its popularity. Before 1600, coffee production was a jealously guarded secret, and fertile beans were not found outside Arabia. Many consider the German botanist Leonhard Rauwolf to have first described coffee in a book published in 1583. Sometime after 1600, coffee trees were grown in India, possibly due to smuggling of fertile beans. Around 1650, coffee importation into England began and coffeehouses opened in Oxford and London. Coffee planting began in the English colonies, but a disease wiped out the plantations, leading the English to re-plant with tea instead.

By the 18th century, the beverage had become popular in Europe, and European colonists had introduced coffee to tropical countries worldwide as a plantation crop to supply domestic demand. At the end of the 19th century, plantations in Brazil alone were producing

over 80% of the world's coffee crop. At the same time, European demand for coffee was so strong that when genuine coffee beans were scarce, people developed similar-tasting substitutes from various roasted vegetable substances, such as chicory root, dandelion root, acorns, or figs. For example, the British used acorns as a coffee substitute during World War II when German U-boats blockaded Britain.

The major coffee-producing countries are Brazil, Colombia, Vietnam, Indonesia, Costa Rica, Mexico, India, and Puerto Rico but coffee is grown in over 70 countries (2003 USDA and ICO data). Major importers are United States, Germany, Japan, France, Italy, and Spain (2002 USDA data), and per-capita consumers of coffee are Finland (11 kg), Denmark (9.7 kg), Norway (9.5 kg), Sweden (8.6 kg), and Austria (7.8 kg). The United States, while the largest importing country, only ranks 16th (4.1 kg) in per-capita consumption (2001 USDA data).

Khat

Conservation status: Least concern (LR/lc)

Scientific classification

Kingdom: Plantae
Division: Magnoliophyta
Class: Magnoliopsida
Order: Celastrales
Family: Celastraceae
Genus: *Catha*
Species: *C. edulis*

Binomial name *Catha edulis (Vahl) Forssk. ex Endl.*

Khat (Catha edulis, family Celastraceae, Ge'ez +u #t; Arabic B-7), pronounced "cot" and also known as *qat*, *gat*, *chat*, and *miraa*, is a flowering plant native to tropical East Africa. Believed to originate in Ethiopia, it is a shrub or small tree growing to 5–8 m tall, with evergreen leaves 5–10 cm long and 1–4 cm broad. The flowers are produced on short axillary cymes 4–8 cm long, each flower small, with five white petals. The fruit is an oblong three-valved capsule containing 1–3 seeds.

Cultivation and uses

Khat has been grown for use as a stimulant for centuries in the Horn of Africa and the Arabian Peninsula. There, chewing khat predates the use of coffee and is used in a similar social context. Its fresh leaves and tops are chewed or, less frequently, dried and consumed as tea, in order to achieve a state of euphoria and stimulation. Due to the availability of rapid, inexpensive air transportation, the drug has been reported in England, Rome, Amsterdam, Canada, Australia and the United States. The public has become more aware of this exotic drug through media reports pertaining to the United Nations mission in Somalia, where khat

use is endemic, and its role in the Persian Gulf. The khat plant is known by a variety of names, such as qat in Yemen, chat in Ethiopia, jaad in Somalia and miraa in Kenya.

Khat use has traditionally been confined to the regions where khat is grown, because only the fresh leaves have the desired stimulating effects. In recent years improved roads, off-road motor vehicles and air transport have increased the global distribution of this perishable commodity. Traditionally, khat has been used as a socializing drug, and this is still very much the case in Yemen where khat-chewing is a predominantly male habit. In other countries, khat is consumed largely by single individuals and at parties. It is mainly a recreational drug in the countries which grow khat, though it may also be used by farmers and laborers for reducing physical fatigue and by drivers and students for improving attention. This is similar to the use of the coca leaf in South America.

Khat is used for its mild euphoric and stimulating effects. Because of its anorectic effects, it is often used by Muslims in Ethiopia to aid in fasting. Today it is also used by Christians though the Ethiopian Orthodox Tewahedo Church (along with its Eritrean counterpart) has forbidden Christians from using it due to its stimulating effects.

The Supreme Islamic Courts Council, which took control of much of the country in 2006, banned khat during Ramadan, sparking street protests in Kismayo. In November 2006, Kenya banned all flights to Somalia, citing security concerns, prompting protests by Kenyan chat growers. The Kenyan MP from Ntonyiri, Meru District stated that local land had been specialized in khat cultivation, that 20 tons worth US$800,000 were shipped to Somalia daily and that a flight ban could devastate the local economy.[1]

Chemistry/pharmacology

The stimulant effect of the plant was originally attributed to cathine, a phenethylamine-type substance isolated from the plant. However, the attribution was disputed by reports showing the plant extracts from fresh leaves contained another substance more behaviorally active than cathine. In 1975, the related alkaloid cathinone was isolated, and its absolute configuration was established in 1978. Cathinone is not very stable and breaks down to produce cathine and norephedrine. These chemicals belong to the PPA (phenylpropanolamine) family, a subset of the phenethylamines related to amphetamines and the catecholamines epinephrine and norepinephrine.

Khat consumption induces mild euphoria and excitement. Individuals become very talkative under the influence of the drug and may appear to be unrealistic and emotionally unstable. Khat can induce manic behaviors and hyperactivity. Several cases of khat-induced psychosis have been reported in the literature. Khat is an effective anorectic and its use also results in constipation. Dilated pupils (mydriasis), which are prominent during khat consumption, reflect the sympathomimetic effects of the drug, which are also reflected in increased heart rate and blood pressure. A state of drowsy hallucinations (hypnagogic hallucinations) may result coming down from khat use as well. Withdrawal symptoms that may follow prolonged khat use include lethargy, mild depression, nightmares, and slight tremor. Long term use can precipitate the following effects: negative impact on liver function, permanent tooth darkening (of a greenish tinge), susceptibility to ulcers, and diminished sex drive. Khat is usually not a addictive drug, although there are some people

who can not stay with out it for more then 4-5 days, feeling tired and having difficulty concentrating.

User population

It is estimated that several million people are frequent users of khat. Many of the users originate from countries between Sudan and Madagascar and in the southwestern part of the Arabian Peninsula, especially Yemen. In Yemen, 60% of the males and 35% of the females were found to be khat users who had chewed daily for long periods of their life. The traditional form of khat chewing in Yemen involves only male users; khat chewing by females is less formal and less frequent. In Saudi Arabia, the cultivation and consumption of khat are forbidden, and the ban is strictly enforced. The ban on khat is further supported by the clergy on the grounds that the Qur'an forbids anything that is harmful to the body. This is in sharp contrast to the opinions of the clergy in Yemen. In Somalia, 61% of the population reported that they do use khat, 18% report habitual use, and 21% are occasional users.

UK

Khat is used by members of the Somali and Yemeni community (mainly men), which is concentrated in London, Birmingham, Bristol, Cardiff, Manchester and Sheffield. It is currently legal in the UK although there are calls from some sections of the Somali community for it to be banned.

Control status

In 1965, the World Health Organization Expert Committee on Dependence-producing Drugs' Fourteenth Report noted, "The Committee was pleased to note the resolution of the Economic and Social Council with respect to khat, confirming the view that the abuse of this substance is a regional problem and may best be controlled at that level". For this reason, khat was not Scheduled under the Single Convention on Narcotic Drugs. In 1980 the World Health Organization classified khat as a drug of abuse that can produce mild to moderate psychic dependence.

Cathine is in Schedule IV and cathinone is in Schedule I of the U.S. Controlled Substance Act. The 1993 DEA rule placing cathinone in Schedule I noted that it was effectively also banning khat:

> Cathinone is the major psychoactive component of the plant Catha edulis (khat). The young leaves of khat are chewed for a stimulant effect. Enactment of this rule results in the placement of any material which contains cathinone into Schedule I.

In the UK, Cathine and Cathinone are Class C drugs. The plant *Catha edulis* is uncontrolled. In Germany, Cathine is a controlled substance, and ownership and sale of the plant is illegal. Similar levels of control exist throughout most other European countries.

In Canada, Khat is a controlled substance under Schedule IV of the Controlled Drugs and Substance Act (CDSA). Every person who seeks or obtain Khat is guilty of an indictable offence and liable to imprisonment for a term not exceeding eighteen months, where the

subject-matter of the offence is a substance included in Schedule IV *or* is guilty of an offence punishable on summary conviction and liable for a first offence, to a fine not exceeding one thousand dollars or to imprisonment for a term not exceeding six months, or to both, and for a subsequent offence, to a fine not exceeding two thousand dollars or to imprisonment for a term not exceeding one year, or to both.

In Australia, the importation of khat is controlled under the Customs (Prohibited Imports) Regulations. Individual users may apply for several required licenses to import up to 5 kg per month for personal use (primarily immigrants from the Horn of Africa). In 2003, the total number of khat annual permits was 294 and the total number of individual khat permits was 202."

"There are two types of import permits. The single use Permit to Import can be used only once and you must request a new permit for each time you wish to import khat. Annual Permits are labeled as such and consist of two pages. Annual Permits allow you to import up to 5 kg once a month for up to twelve months."

Trivia

- The word "qat" is well known to Scrabble players as a way to use the Q when no U is available.
- Smuggling of the plant known as Qhat (Khat) is the main reason British nationals require consular assistance in Canada.

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Notes

1. ^ "Kenya bans all flights to Somalia"**, BBC News, 13 November 2006**

Tea

Tea is a beverage made by steeping processed leaves, buds or twigs of the tea bush Camellia sinensis in hot water for a few minutes. The processing can include oxidation (fermentation), heating, drying and the addition of other herbs, flowers, spices and fruits.

There are four types of true tea: black tea, oolong tea, green tea, and white tea. The term herbal tea usually refers to infusions of fruit or herbs such as rosehip tea, chamomile tea and Jiaogulan that contain no tea leaves. (Alternative terms for herbal tea that avoid the word "tea" are tisane and herbal infusion). This article is concerned exclusively with preparations and uses of the tea plant Camellia sinensis.

Tea is a natural source of caffeine, theophylline, theanine, and antioxidants, but it has almost no fat, carbohydrates, or protein. It has a cooling, slightly bitter and astringent taste.

Processing and classification

The types of tea are distinguished by their processing. Leaves of Camellia sinensis, if not dried quickly after picking, soon begin to wilt and oxidize. This process resembles the malting of barley, in that starch is converted into sugars; the leaves turn progressively darker, as chlorophyll breaks down and tannins are released. The next step in processing is to stop the oxidation process at a predetermined stage by taking the water from the leaves via heating.

The term fermentation was used (probably by wine fanciers) to describe this process, and has stuck, even though no true fermentation happens (i.e., the process is not driven by yeast and produces no ethanol). Without careful moisture and temperature control, however, fungi will grow on tea. The fungi cause real fermentation which will contaminate the tea with toxic and carcinogenic substances, so that the tea must be discarded.

Tea is traditionally classified based on the degree or period of fermentation (oxidation) the leaves have undergone:

White tea Young leaves (new growth buds) that have undergone no oxidation; the buds may be shielded from sunlight to prevent formation of chlorophyll. White tea is produced in lesser quantities than most of the other styles, and can be correspondingly more expensive than tea from the same plant processed by other methods. It is also less well-known in countries outside of China, though this is changing with increased western interest in organic or premium teas.

Green tea The oxidation process is stopped after a minimal amount of oxidation by application of heat; either with steam, a traditional Japanese method; or by dry cooking in hot pans, the traditional Chinese method. Tea leaves may be left to dry as separate leaves are rolled into small pellets to make gun-powder tea. The latter process is time-consuming and is typically done only with pekoes of higher quality. The tea is processed within one to two days of harvesting.

Oolong Oxidation is stopped somewhere between the standards for green tea and black tea. The oxidation process will take two to three days.

Black tea/Red tea The tea leaves are allowed to completely oxidize. Black tea is the most common form of tea in southern Asia (India, Sri Lanka, Bangladesh, Pakistan etc) and in the last century many African countries including Kenya, Burundi, Rwanda, Malawi and Zimbabwe. The literal translation of the Chinese word is red tea, which may be used by some tea-lovers. The Chinese call it red tea because the actual tea liquid is red. Westerners call it black tea because the tea leaves used to brew it are usually black. However, red tea may also refer to rooibos, an increasingly popular South African tisane. The oxidation process will take around two weeks and up to one month. Black tea is further classified as either orthodox or CTC (Crush, Tear, Curl, a production method developed about 1932). Unblended black teas are also identified by the estate they come from, their year and the flush (first, second or autumn). Orthodox and CTC teas are further graded according to the post-production leaf quality by the Orange Pekoe system.

Pu-erh (also known as Póu léi (Polee) in Cantonese), Two forms of pu-erh teas are available, "raw" and "ripened". "Raw" or "green" pu-erh may be consumed young or aged to further mature. During the aging process, the tea undergoes a second, microbial fermentation. "Ripened" pu-erh is made from green pu-erh leaf that has been artificially oxidized to approximate the flavour of the natural aging process. This is done through a controlled process similar to composting, where both the moisture and temperature of the tea are carefully monitored. Both types of pu-erh tea are usually compressed into various shapes including bricks, discs, bowls, or mushrooms. While most teas are consumed within a year of production, pu-erh can be aged for many years to improve its flavour, up to 30 to 50 years for raw pu-erh and 10 to 15 years for ripened pu-erh, although experts and aficionados disagree about what the optimal age is to stop the aging process. Most often, pu-erh is steeped for up to five minutes in boiling water. Additionally, some Tibetans use pu-erh as a caloric food, boiled with yak butter, sugar and salt to make yak butter tea. Teas that undergo a second oxidation, such as pu-erh and liu bao, are collectively referred to as black tea in Chinese. This is not to be confused with the English term Black tea, which is known in Chinese as red tea.

Yellow tea Either used as a name of high-quality tea served at the Imperial court, or of special tea processed similarly to green tea, but with a slower drying phase.

Kukicha Also called winter tea, kukicha is made from twigs and old leaves pruned from the tea plant during its dormant season and dry-roasted over a fire. It is popular as a health food in Japan and in macrobiotic diets.

Genmaicha Literally "brown rice tea" in Japanese, a green tea blended with dry-roasted brown rice (sometimes including popped rice), very popular in Japan but also drunk in China.

Flower tea Teas processed or brewed with flowers; typically, each flower goes with a specific category of tea, such as green or red tea. The most famous flower tea is jasmine tea (hua chá, literally "flower tea," in Mandarin; heung pín in Cantonese), a green or oolong tea scented (or brewed) with jasmine flowers. Chrysanthemum, osmanthus, lotus, rose, and lychee are also popular flowers.

Blending and additives

Almost all teas in bags and most other teas sold in England are blends. Blending may occur at the level of tea-planting area (e.g., Assam), or teas from many areas may be blended. The aim of blending is a stable taste over different years, and a better price. More expensive, better tasting tea may cover the inferior taste of cheaper tea.

There are various teas which have additives and/or different processing than "pure" varieties. Tea is able to easily receive any aroma, which may cause problems in processing, transportation or storage of tea, but can be also advantageously used to prepare scented teas.

Content

Tea contains catechins, a type of antioxidant. In fresh tea leaf, catechins can be up to 30% of the dry weight. Catechins are highest in concentration in white and green teas while black tea has substantially less due to its oxidative preparation. Tea also contains the stimulants

caffeine (about 3% of the dry weight and typically 40 mg per cup of prepared tea), theophylline and theobromine, the latter two being present in very small amounts.[1]

Origin and early history in Asia

The cradle of the tea plant is a region that encompasses eastern and southern China, northern Myanmar, and the Assam state of India. Spontaneous (wild) growth of the assamica variant is observed in area ranging from Chinese province Yunnan to the northern part of Myanmar and Assam region of India. The variant sinensis grows naturally in eastern and southeastern regions of China.[2] Recent studies and occurrence of hybrids of the two types in wider area extending over mentioned regions suggest the place of origin of tea is in an area consisting of the northern part of Myanmar and the Yunnan and Sichuan provinces of China.[3]

Origins of human use of tea are described in several myths, but it is unknown as to where tea was first created as a drink.

Creation myths

In one popular Chinese legend, Shennong, the legendary Emperor of China, inventor of agriculture and Chinese medicine, was on a journey about five thousand years ago. The Emperor, known for his wisdom in the ways of science, believed that the safest way to drink water was by first boiling it. One day he noticed some leaves had fallen into his boiling water. The ever inquisitive and curious monarch took a sip of the brew and was pleasantly surprised by its flavour and its restorative properties. Variant of the legend tells that the emperor tried medical properties of various herbs on himself, some of them poisonous, and found tea works as an antidote.[4] Shennong is also mentioned in Lu Yu's Cha Jing, famous early work on the subject.[5]

A Chinese legend, which spread along with Buddhism, Bodhidharma is credited with discovery of tea. Bodhidharma, a semi-legendary Buddhist monk, founder of the Chan school of Buddhism, journeyed to China. He became angered because he was falling asleep during meditation, so he cut off his eyelids. Tea bushes sprung from the spot where his eyelids hit the ground.[6] Sometimes, the second story is retold with Gautama Buddha in place of Bodhidharma[7] In another variant of the first mentioned myth, Gautama Buddha discovered tea when some leaves had fallen into boiling water.[8]

China

Whether or not these legends have any basis in fact, tea has played a significant role in Asian culture for centuries as a staple beverage, a curative, and a symbol of status. It is not surprising its discovery is ascribed to religious or royal origins. The fact is that the Chinese have enjoyed tea for centuries. Scholars hailed the brew as a cure for a variety of ailments, the nobility considered the consumption of good tea as a mark of their status and the common people simply enjoyed its flavour.

While historically the origin of tea as a medicinal herb useful for staying awake is unclear, China is considered the birthplace of tea drinking with recorded tea use in its history to at least 1000 BC. The Han Dynasty used tea as medicine. The use of tea as a beverage drunk for pleasure on social occasions dates from the Tang Dynasty or earlier.

The Tang Dynasty writer Lu Yu's x½ (729-804) Cha Jing 6" is an early work on the subject. According to Cha Jing written around 760, tea drinking was widespread. The book describes how tea plants were grown, the leaves processed, and tea prepared as a beverage. It also describes how tea was evaluated. The book even discusses where the best tea leaves were produced.

At this time in tea's history, the nature of the beverage and style of tea preparation were quite different from the way we experience tea today. Tea leaves were processed into cakes. The dried teacake, generally called brick tea was ground in a stone mortar. Hot water was added to the powdered teacake, or the powdered teacake was boiled in earthenware kettles then consumed as a hot beverage.

A form of compressed tea referred to as white tea was being produced as far back as the Tang Dynasty (618-907 A.D.). This special white tea of Tang was picked in early spring when the new growths of tea bushes that resemble silver needles were abundant. These "first flushes" were used as the raw material to make the compressed tea.

Advent of steaming and powder tea

During the Song Dynasty (960-1279), production and preparation of all tea changed. The tea of Song included many loose-leaf styles (to preserve the delicate character favoured by the court society), but a new powdered form of tea emerged. Tea leaves were picked and quickly steamed to preserve their colour and fresh character. After steaming, the leaves were dried. The finished tea was then ground into fine powders that were whisked in wide bowls. The resulting beverage was highly regarded for its deep emerald or iridescent white appearance and its rejuvenating and healthy energy. Drinking tea was considered stylish among government officers and intellectuals during the Southern Song period in China (12th to 13th centuries). They would read poetry, write calligraphy, paint, and discuss philosophy, while enjoying tea. Sometimes they would hold tea competitions where teas and tea instruments were judged. When Song Dynasty emperor Hui Zhong proclaimed white tea to be the culmination of all that is elegant, he set in motion the evolution of an enchanting variety.

This Song style of tea preparation incorporated powdered tea and ceramic ware in a ceremonial aesthetic known as the Song tea ceremony. Japanese monks traveling to China at this time had learned the Song preparation and brought it home with them. Although it later became extinct in China, this Song style of tea evolved into the Japanese tea ceremony, which endures today.

Many forms of white tea were made in the Song Dynasty due to the discerning tastes of the court society. Hui Zhong, who ruled China from 1101-1125, referred to white tea as the best type of tea, and he has been credited with the development of many white teas in the Song Dynasty, including "Palace Jade Sprout" and "Silver Silk Water Sprout".

Producing white teas was extremely labour-intensive. First, tea was picked from selected varietals of cultivated bushes or wild tea trees in early spring. The tea was immediately steamed, and the buds were then selected and stripped of their outer, unopened leaf. Only the delicate interior of the bud was reserved to be rinsed with spring water and dried. This process produced white teas that were paper thin and small.

Once processed, the finished tea was distributed and often given as a tribute to the Song court in loose form. It was then ground to a fine, silvery-white powder that was whisked in the wide ceramic bowls used in the Song tea ceremony. These white powder teas were also used in the famous whisked tea competitions of that era.

Roasting and brewing

Steaming tea leaves was the primary process used for centuries in the preparation of tea. After the transition from compressed tea to the powdered form, the production of tea for trade and distribution changed once again. The Chinese learned to process tea in a different way in the mid-13th century. Tea leaves were roasted and then crumbled rather than steamed. This is the origin of today's loose teas and the practice of brewed tea.

In 1391, the Ming court issued a decree that only loose tea would be accepted as a "tribute". As a result, loose tea production increased and processing techniques advanced. Soon, most tea was distributed in full-leaf, loose form and steeped in earthenware vessels.

Oxidization (often mistakenly called fermentation)

Tea "fermentation" is not related to yeast fermentation. It is actually the oxidization of the tea leaves. In 17th century China numerous advances were made in tea production. In the southern part of China, tea leaves were sun dried then half fermented, producing Black Dragon teas or Oolongs. However, this method was not common in the rest of China.

Korea

The first historical record documenting the offering of tea to an ancestral god describes a rite in the year 661 in which a tea offering was made to the spirit of King Suro, the founder of the Geumgwan Gaya Kingdom (42-562).

Records from the Goryeo Dynasty (918-1392) show that tea offerings were made in Buddhist temples to the spirits of revered monks.

During the Joseon Dynasty (1392-1910), the royal Yi family and the aristocracy used tea for simple rites, the "Day Tea Rite" was a common daytime ceremony, whereas the "Special Tea Rite" was reserved for specific occasions. These terms are not found in other countries. Toward the end of the Joseon Dynasty, commoners joined the trend and used tea for ancestral rites, following the Chinese example based on Zhu Xi's text formalities of Family.

Stoneware was common, ceramic more frequent, mostly made in provincial kilns, with porcelain rare, imperial porcelain with dragons the rarest.

Historically the appearance of the bowls and cups is naturalistic, with a division according to religious influence. Celadon or jade green, "punchong", or bronze-like weathered patinas for Buddhist tea rituals; the purest of white with faint designs in porcelain for Confucian tea rituals; and coarser porcelains and ash-stone glazes for animist tea rituals, or for export to Japan where they were known as "gohan chawan". An aesthetic of rough surface texture from a clay and sand mix with a thin glazing were particularly prized and copied. The randomness of this creation was said to provide a "now moment of reality" treasured by tea masters.

Unlike the Chinese tradition, no Korean tea vessels used in the ceremony are tested for a fine musical note. Judgment instead is based on naturalness in form, emotion, and colouring.

The earliest kinds of tea used in tea ceremonies were heavily pressed cakes of black tea, the equivalent of aged pu-erh tea still popular in China. Vintages of tea were respected, and tea of great age imported from China had a certain popularity at court. However, importation of tea plants by Buddhist monks brought a more delicate series of teas into Korea, and the tea ceremony.

While green tea, "chaksol" or "chugno", is most often served, other teas such as "Byeoksoryung" Chunhachoon, Woojeon, Jakseol, Jookro, Okcheon, as well as native chrysanthemum tea, persimmon leaf tea, or mugwort tea may be served at different times of the year.

Buddhist monks incorporated tea ceremonies into votive offerings. However the Goryeo nobility and later the Confucian yangban scholars formalized the rituals. Tea ceremonies have always been used for important occasions such as birthdays, anniversaries, remembrance of old friends, and increasingly a way to rediscovering Seon meditation.

Japanese Involvement

Importing tea and tea culture

The earliest known references to green tea in Japan are in a text written by a Buddhist monk in the 9th century. Tea became a drink of the religious classes in Japan when Japanese priests and envoys sent to China to learn about its culture brought tea to Japan. The first form of tea brought from China was probably in a teacake. Ancient recordings indicate the first batch of tea seeds were brought by a priest named Saicho („; 767-822) in 805 and then by another named Kukai (zw; 774-835) in 806. It became a drink of the royal classes when Emperor Saga (oè)‡), the Japanese emperor, encouraged the growth of tea plants. Seeds were imported from China, and cultivation in Japan began.

Kissa Yojoki - the Book of Tea

In 1191, the famous Zen priest Eisai (; 1141-1215) brought back tea seeds to Kyoto. Some of the tea seeds were given to the priest Myoe Shonin, and became the basis for Uji tea. The oldest tea specialty book in Japan, Kissa Yojoki («6 ; how to stay healthy by drinking tea) was written by Eisai. The two-volume book was written in 1211 after his second and last visit to China. The first sentence states, "Tea is the ultimate mental and medical remedy and has the ability to make one's life more full and complete". The preface describes how drinking tea can have a positive effect on the five vital organs, especially the heart. It discusses tea's medicinal qualities which include easing the effects of alcohol, acting as a stimulant, curing blotchiness, quenching thirst, eliminating indigestion, curing beriberi, preventing fatigue, and improving urinary and brain function. Part One also explains the shapes of tea plants, tea flowers and tea leaves and covers how to grow tea plants and process tea leaves. In Part Two, the book discusses the specific dosage and method required for individual physical ailments.

Eisai was also instrumental in introducing tea consumption to the warrior class, which rose to political prominence after the Heian Period. Eisai learned that the shogun Minamoto no Sanetomo had a habit of drinking too much every night. In 1214, Eisai presented a book he had written to the general, lauding the health benefits of tea drinking. After that, the custom of tea drinking became popular among the Samurai.

Very soon, green tea became a staple among cultured people in Japan -- a brew for the gentry and the Buddhist priesthood alike. Production grew and tea became increasingly accessible, though still a privilege enjoyed mostly by the upper classes.

Roasting process introduced to Japan

In the 13th century Ming dynasty, southern China and Japan enjoyed much cultural exchange. Significant merchandise was traded and the roasting method of processing tea became common in Kyushu, Japan. Since the steaming (9th century) and the roasting (13th century) method were brought to Japan during two different periods, these teas are completely distinct from each another.

Japan tea culture emerges

The pastime made popular in China in the twelfth and thirteenth centuries -- reading poetry, writing calligraphy, painting, and discussing philosophy while enjoying tea – eventually became popular in Japan and with Samurai society. The modern tea ceremony developed over several centuries by Zen Buddhist monks under the original guidance of the monk Sen-no Rikyu (1522-1591). In fact, both the beverage and the ceremony surrounding it played a prominent role in feudal diplomacy. Many of the most important negotiations among feudal clan leaders were carried out in the austere and serene setting of the tea ceremony. By the end of the sixteenth century, the current "Way of Tea" was established. Eventually, green tea became available to the masses, making it the nation's most popular beverage.

Modern Japanese green tea

In 1738, Soen Nagatani developed Japanese sencha (Japanese: N6), which is an unfermented form of green tea. To prepare sencha, tea leaves are first steam-pressed, then rolled and dried into a loose tea.

In 1835, Kahei Yamamoto developed gyokuro (Japanese: ‰2), considered the finest loose-leaf Japanese green tea, by shading tea trees during the weeks leading up to harvesting in order to alter the leaf chemistry in ways considered pleasant by most green tea drinkers.

Modern maccha (Japanese: ¹6) is normally taken from the same shaded trees as gyokuro and ground to a fine powder to be mixed whole into hot water, and is the tea used in the Japanese tea ceremony.

Rolling machines

At the end of the Meiji period (1868-1912), machine manufacturing of green tea was introduced and began replacing handmade tea. Machines took over the processes of primary drying, tea rolling, secondary drying, final rolling, and steaming.

Automation

Automation contributed to improved quality control and reduced labour. Sensor and computer controls were introduced to machine automation so that unskilled workers can produce superior tea without compromising in quality. Certain regions in Japan are known for special types of green tea, as well as for teas of exceptional quality, making the leaves themselves a highly valued commodity. This combination of Nature's bounty and manmade technical breakthroughs combine to produce the most exceptional green tea products sold on the market today. Today, roasted green tea is not as common in Japan and powdered tea is used in ceremonial fashion.

Tea spreads to the world

As the Venetian explorer Marco Polo failed to mention tea in his travel records, it is conjectured that the first Europeans to encounter tea were either Jesuits living in Beijing who attended the court of the last Ming Emperors; or Portuguese explorers visiting Japan in 1560. Russia discovered tea in 1618 after a Ming Emperor of China offered it as a gift to Czar Michael I.

Soon imported tea was introduced to Europe, where it quickly became popular among the wealthy in France and the Netherlands. English use of tea dates from about 1650 and is attributed to Catherine of Braganza (Portuguese princess and queen consort of Charles II of England).

The high demand for tea in Britain caused a huge trade deficit with China, leading the British to try to produce their own in the mid-nineteenth century. Using seeds smuggled from China (there was an official ban on foreigners entering tea-growing areas), the British went through some failed experiments but finally succeeded in setting up productive plantations in parts of colonial India with suitable climates and soil.[9][10] They also tried to balance the trade deficit by selling opium to the Chinese, which later led to the First Opium War in 1838–1842.

The Boston Tea Party was an act of uprising in which Boston residents destroyed crates of British tea in 1773, in protest against British tea and taxation policy. Prior to the Boston Tea Party, residents of Britain's North American 13 colonies drank far more tea than coffee. In Britain, coffee was more popular. After the protests against the various taxes, British Colonists stopped drinking tea as an act of patriotism. Similarly, Britons slowed their consumption of coffee.

Iced Tea has been popular in North America since the 1904 St. Louis World's Fair.

These days, contradicting tea economies do exist. Tea farmers in Japan, Taiwan and China often enjoy better incomes compared to farmers in black tea producing countries.

The word tea

The Chinese character for tea is 6, but it is pronounced differently in the various Chinese dialects. Two pronunciations have made their way into other languages around the world. One is 'te' (Taiwanese (linguistics): tê) which comes from the Min Nan dialect spoken around the port of Xiamen (Amoy). The other is Chá, used by the Cantonese dialect spoken around the ports of Guangzhou (Canton), Hong Kong, Macau, and in overseas Chinese communities, as well as in the Mandarin dialect of northern China. Yet another different pronunciation is 'zu', used in the Wu dialect spoken around Shanghai.

Languages that have Te derivatives include Afrikaans (tee), Armenian, Catalan (te), Czech (té or thé, but these words sound archaic, aj is used nowadays, see the next paragraph), Danish (te), Dutch (thee), English (tea), Esperanto (teo), Estonian (tee), Faroese (te), Finnish (tee), French (thé), (West) Frisian (tee), Galician (té), German (Tee), Hebrew (êÔ, /te/ or /tei/), Hungarian (tea), Icelandic (te), Indonesian (teh), Irish (tae), Italian (tè), scientific Latin (thea), Latvian (tja), Malay (teh), Norwegian (te), Polish (herbata from Latin herba thea), Scots Gaelic (tì, teatha), Singhalese, Spanish (té), Swedish (te), Tamil (thè), Welsh (te), and Yiddish (ØÙÙ, /tei/).

Those that use Cha or Chai derivatives include Albanian (çaj), Arabic (4N'J/shi/chai), Assyrian (pronounced chai), Azeri: (çay), Bengali (š¾), Bosnian (aj), Bulgarian (G09), Capampangan (cha), Cebuano (tsa), Croatian (aj), Czech (aj), Greek (ÄÃ¬¹), Hindi (>/)chai, Japanese (6, aʃ, cha), Kazakh (H09), Korean ((), Macedonian (aj), Malayalam, Nepali (chai), Persian (†'I), Punjabi (>9), Portuguese (chá), Romanian (ceai), Russian, (G09, chai), Serbian (G0X), Slovak (aj), Slovene (aj), Somali (shaax), Swahili (chai), Tagalog (tsaa), Thai (2), Tibetan (ja), Turkish (çay), Ukrainian (G09), Urdu (†'I), Uzbek (choy) and Vietnamese (trà and chè are both direct derivatives of the Chinese 6; the latter term is used mainly in the north).

The Polish word for a tea-kettle is czajnik, which could be derived directly from Cha or from the cognate Russian word. However, tea in Polish is herbata, which was probably derived from the Latin herba thea, meaning "tea herb".

It is tempting to correlate these names with the route that was used to deliver tea to these cultures, although the relation is far from simple at times. As an example, the first tea to reach Britain was traded by the Dutch from Fujian, which uses te, and although later most British trade went through Canton, which uses cha, the Fujianese pronunciation continued to be the more popular.

In Ireland, or at least in Dublin, the term "cha" is sometimes used for tea, with "tay" as a common pronunciation throughout the land (derived from the Irish Gaelic tae), and "char" was a common slang term for tea throughout British Empire and Commonwealth military forces in the 19th and 20th centuries, crossing over into civilian usage. In North America, the word "chai" is used to refer almost exclusively to the Indian "chai" (or "masala chai") beverage.

Perhaps the only place in which a word unrelated to tea is used to describe the beverage is South America (particularly Andean countries), because a similar stimulant beverage,

hierba mate, was consumed there long before tea arrived. In various places of South America, any tea is referred to as mate.

Tea culture

Tea is often drunk at social events, such as afternoon tea and the tea party. It may be drunk early in the day to heighten alertness; it contains theophylline and bound caffeine (sometimes called "theine"), although there are also decaffeinated teas.

There are tea ceremonies which have arisen in different cultures, Japan's complex, formal and serene one being the most known. Other examples are the Korean tea ceremony or some traditional ways of brewing tea in Chinese tea culture.

Preparation

This section describes the most widespread method of making tea. Completely different methods are used in North Africa, Tibet and perhaps in other places. In the American South, iced tea is also prepared differently.

The best way to prepare tea is usually thought to be with loose tea placed either directly in a teapot or contained in a tea infuser, rather than a teabag. However, perfectly acceptable tea can be made with teabags. Some circumvent the teapot stage altogether and brew the tea directly in a cup or mug. This method is becoming more popular. For an acceptable quality, however, it is necessary to obey the rules for preparation such as sufficient infusion time by placing the teabag in the cup before pouring the hot water.

Historically in China, tea is divided into a number of infusions. The first infusion is immediately poured out to wash the tea, and then the second and further infusions are had. The third through fifth are nearly always considered the best infusions of tea, although different teas open up differently and may require more infusions of boiling water to bring them to life.

Typically, the best temperature for brewing tea can be determined by its type. Teas that have little or no oxidation period, such as a green or white tea, are best brewed at lower temperatures around 80 °C, while teas with longer oxidation periods should be brewed at higher temperatures around 100 °C.

Black tea The water for black teas should be added at the boiling point (100 °C or 212 °F), except for more delicate teas, where lower temperatures are recommended. This will have as large an effect on the final flavour as the type of tea used. The most common fault when making black tea is to use water at too low a temperature. Since boiling point drops with increasing altitude, this makes it difficult to brew black tea properly in mountainous areas. It is also recommended that the teapot be warmed before preparing tea, easily done by adding a small amount of boiling water to the pot, swirling briefly, before discarding. Black tea should not be allowed to steep for less than 30 seconds or more than about five minutes (a process known as brewing or [dialectally] mashing in the UK). After that, tannin is released, which counteracts the stimulating effect of the theophylline and caffeine and makes the tea bitter (at this point it is referred to as being stewed in the UK). Therefore, for a "wake-up" tea, one should not let the tea steep for more than 2- 3minutes. When the tea has brewed long enough to suit the tastes of the drinker, it should be strained while serving.

Green tea Water for green tea, according to most accounts, should be around 80 °C to 85 °C (176 °F to 185 °F); the higher the quality of the leaves, the lower the temperature. Hotter water will burn green-tea leaves, producing a bitter taste. Preferably, the container in which the tea is steeped, the mug, or teapot should also be warmed beforehand so that the tea does not immediately cool down.

Oolong tea Oolong teas should be brewed around 90 °C to 100 °C (194 °F to 212 °F), and again the brewing vessel should be warmed before pouring in the water. Yixing purple clay teapots are the ideal brewing vessel for oolong tea. For best results use spring water, as the minerals in spring water tend to bring out more flavour in the tea.

Premium or delicate tea Some teas, especially green teas and delicate Oolong or Darjeeling teas, are steeped for shorter periods, sometimes less than 30 seconds. Using a tea strainer separates the leaves from the water at the end of the brewing time if a tea bag is not being used.

Serving In order to preserve the pre-tannin tea without requiring it all to be poured into cups, a second teapot is employed. The steeping pot is best unglazed earthenware; Yixing pots are the best known of these, famed for the high quality clay from which they are made. The serving pot is generally porcelain, which retains the heat better. Larger teapots are a post-19th-century invention, as tea before this time was very rare and very expensive. Experienced tea-drinkers often insist that the tea should not be stirred around while it is steeping (sometimes called winding in the UK). This, they say, will do little to strengthen the tea, but is likely to bring the tannic acids out in the same way that brewing too long will do. For the same reason one should not squeeze the last drops out of a teabag; if stronger tea is desired, more tea leaves should be used.

Additives The addition of other items such as milk and sugar to tea is primarily a European invention[11], though it has also spread to british colonies such as Hong Kong[12] or India. Some connoisseurs eschew cream because it overpowers the flavour of tea. Many teas are traditionally drunk with milk. These include Indian chai, and British tea blends. These teas tend to be very hearty varieties which can be tasted through the milk, such as Assams, or the East Friesian blend. Milk is thought to neutralise remaining tannins and reduce acidity.

When taking milk with tea, some add the tea to the milk rather than the other way around when using chilled milk; this avoids scalding the milk, leading to a better emulsion and nicer taste.[13] The socially 'correct' order is tea, sugar, milk, but this convention was established before the invention of the refrigerator. It is worth noting that this convention was only universally established in the 20th century - prior to this, the common earthenware mugs used were unable to withstand the temperature of the tea, and so the convention was to add the tea to the milk. This was not the case with bone china. Adding the milk first also makes a milkier cup of tea with sugar harder to dissolve as there will be no hot liquid in the cup. In addition, the amount of milk used is normally determined by the colour of the tea, therefore milk is added until the correct colour is obtained. If the milk is added first, more guesswork is involved. If the tea is being brewed in a mug, the milk is generally added after the tea bag is removed (however, it is arguably better to add milk before removing the tea bag than it is to remove the tea bag too soon: the tea will continue to brew even with milk added). Other popular additives to tea include sugar or honey, lemon, and fruit jams. In colder regions such as Mongolia and Nepal, butter is added to provide necessary calories. Tibetan butter tea

contains rock salt and yak butter, which is then churned vigorously in a cylindrical vessel closely resembling a butter churn. The flavour of this beverage is more akin to a rich broth than to tea, and may be described as a very acquired taste to those unused to drinking it.

Ceremony Zen Buddhism is the root of the highly refined Japanese tea ceremony. The Chinese province of Fujian is the origin of the Gong Fu tea ceremony, which is unrelated to the martial art called Kung Fu though the characters are the same: literally "time-energy" or something which takes a lot of time and energy. It features the rapid use of tongs and various vessels to make tea. Loose leaf tea venders in China often use this method to make tea for their customers. The Korean Tea Ceremony is more like the Chinese ceremony. In the United Kingdom, adding the milk first is historically considered a lower-class method of preparing tea; the upper classes always add the milk last. The origin of this distinction is said to be that the rougher earthenware mugs of the working class would break if boiling-hot tea was added directly to them, whereas the fine glazed china cups of the upper class would not. It is now considered by most to be a personal preference.

Packaging

Tea bags Tea leaves are packed into a small (usually paper) tea bag. It is easy and convenient, making tea bags popular for many people nowadays. However, because fannings and dust from modern tea processing are also included in most tea bags, it is commonly held among tea aficionados that this method provides an inferior taste and experience. The paper used for the bag can also be tasted by many which can detract from the tea's flavour. Additional reasons why bag tea is considered less well-flavoured include:

- Dried tea loses its flavour quickly on exposure to air. Most bag teas (although not all) contain leaves broken into small pieces; the great surface-area-to-volume ratio of the leaves in tea bags exposes them to more air, and therefore causes them to go stale faster. Loose tea leaves are likely to be in larger pieces, or to be entirely intact.
- Breaking up the leaves for bags extracts flavoured oils.
- The small size of the bag does not allow leaves to diffuse and steep properly.

Triangle Tea Bags A new infuser has recently come onto the market with an unusual design. The mesh triangle bags are made of a gossamer mesh and have been criticized of being environmentally unfriendly. The shape is designed to allow the tea leaves to expand more when steeping, and not leave flavours (such as paper) in the tea, addressing two of connoisseurs' arguments against tea bags. As such, the flavours available tend towards more gourmet selections such as white tea rather than blends.

Loose tea The tea leaves are packaged loosely in a canister or other container. The portions must be individually measured by the consumer for use in a cup, mug or teapot. This allows greater flexibility, letting the consumer brew weaker or stronger tea as desired, but convenience is sacrificed. Strainers, "tea presses", filtered teapots and infusion bags are available commercially to avoid having to drink the floating loose leaves. A more traditional, yet perhaps more effective way around this problem is to use a three-piece lidded teacup,

called a gaiwan. The lid of the gaiwan can be tilted to decant the leaves while pouring the tea into a different cup for consumption.

Compressed tea A lot of tea is still compressed for storage and aging convenience. Commonly Pu-Erh tea is compressed and then drunk by loosening leaves off using a small knife. Most of the time compressed tea can be stored longer than loose leaf tea.

Tea sticks One of the more modern forms of tea consumption, an alternative to the tea bag, is tea sticks. The first known tea sticks originated in Holland in the mid 1990's, where a company by the name of Venezia Trading produced a tea stick named Ticolino. Ticolino are dubbed as single serving tea sticks which use an infusing technology to brew the tea leaves inside, releasing the flavour and aroma.

Instant tea In recent times, "instant teas" are becoming popular, similar to freeze dried instant coffee. Instant tea was developed in the 1930's, but not commercialized until the late 1950's, and is only more recently becoming popular. These products often come with added flavours, such as vanilla, honey or fruit, and may also contain powdered milk. Similar products also exist for instant iced tea, due to the convenience of not requiring boiling water. Tea connoisseurs tend to criticise these products for sacrificing the delicacies of tea flavour in exchange for convenience.

Storage

Tea storage is essential to keeping the taste of tea pure. Tea absorbs moisture and odours very easily so it is necessary to keep it in some kind of container away from strong odours. One way to store a small amount of loose leaf tea is to keep it in a tin or glass container. These containers will keep the tea free from moisture and also keep odours out so the tea will keep its original flavour. Other ways to store tea include air tight bags. When storing the tea keep it away from sun light, strong odours, and moisture. For larger amounts of tea it would be good to put it into a cooler type of container. First wrap the tea in brown paper then wrap the paper again with brown paper to keep out any moisture. Then place the tea into a cooler that has nothing in and has a good seal. Next take the tea to a cool place away from moisture and odours. The length of time you can store tea depends on its type. Some teas such as flower teas will go bad in a month or so, but others may get better with age.

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Yerba mate

Conservation status: Near threatened (LR/nt)

Scientific classification

Kingdom: Plantae
Division: Magnoliophyta
Class: Magnoliopsida
Order: Aquifoliales
Family: Aquifoliaceae
Genus: Ilex
Species: *I. paraguariensis*

Binomial name Ilex paraguariensis

Yerba mate (Rioplatense Spanish) or *erva mate* (Portuguese) (Ilex paraguariensis) is a species of holly (family Aquifoliaceae) native to subtropical South America in Argentina,

southern Paraguay, southern Uruguay and southern Brazil and Bolivia. The infusion called mate is prepared by steeping the dried leaves in hot water rather than boiling water like tea or coffee. It is slightly less potent than coffee and much gentler on the stomach. Drinking mate with friends from a shared hollow gourd (also called a mate in Spanish, or cabaça or cuia in Portuguese) with a metal straw (a bombilla in Spanish, bomba or canudo in Portuguese) is an extremely common social practice in Argentina, Uruguay, southern Paraguay, the east side of Chile and southern Bolivia and Brazil. Its use has also been introduced into Lebanon and Syria, particularly among the Alawi and Druze minority.

The flavor of brewed yerba mate is strongly vegetal, herbal, and grassy, reminiscent of some varieties of green tea, though the flavor is much stronger than green tea can achieve. Many consider the flavor to be very agreeable, however, it is generally bitter if steeped in water at boiling point and is traditionally made using boiling water combined with a little cold water. Unlike most teas, it does not become bitter and astringent when steeped for extended periods, and the leaves may be infused several times. Additionally, one can purchase flavored mate, in orange, raspberry, strong, and gentle flavorings.

In Brazil, a toasted version of mate, known as chá mate or "mate tea", is sold in teabag and loose form, and served, sweetened, in specialized shops, either hot or iced with fruit juice or milk. An iced, sweetened version of toasted mate is sold as an uncarbonated soft drink, with or without fruit flavoring. The toasted variety of mate has less of a bitter flavor and more of a spicy fragrance. It is more popular in the coastal cities of Brazil, as opposed to the far southern states where it is consumed in the traditional way (green, drunk with a silver straw from a shared gourd).

The yerba mate plant is a shrub or small tree growing up to 15 meters tall. The leaves are evergreen, 7–11 cm long and 3–5.5 cm wide, with a serrated margin. The flowers are small, greenish-white, with four petals. The fruit is a red berry 4–6 mm diameter.

Nomenclature

The pronunciation of yerba mate in standard Spanish is [È_[r²a Èmate]. The Rioplatense dialect spoken in most of Argentina turns the first sound in yerba into a postalveolar fricative, giving [Èʃ[r²a] in regions closer to Buenos Aires, gradually blending into [È'[r²a] as one goes farther from the city, and eventually to [d'[r²a] around Mendoza. The word hierba is Spanish for grass or herb; yerba is a variant spelling of it which is quite common in Argentina. Mate is from the Quechua mati, meaning "cup". Yerba mate is therefore literally the "cup herb".

The (Brazilian) Portuguese name is erva mate [È[rva Èmati] (also pronounced as [È[rva Èmate] in some regions) and is known coloquially as chimarrão (when taken hot) or tereré (when taken cold). The name given to the plant in Guaraní, language of the indigenous people who first cultivated and enjoyed yerba mate, is ka'a, which has the same meaning as yerba.

Mate is often written maté in English to indicate that the pronunciation is not the same as the much more common English word "mate", by analogy with words of French origin such as "café" and other words whose é distinguishes their pronunciation from otherwise identically spelled English words, such as résumé and resume. Linguistic prescriptivists regard this usage as erroneous, a case of hypercorrection. Purely descriptive linguists regard this sort of usage as a natural evolution of the language.

Cultivation

The plant is grown mainly in South America, more specifically in, Northern Argentina (Corrientes, Misiones), Paraguay, Uruguay and southern Brazil (Rio Grande do Sul and Paraná). The Guaraní are reputed to be the first people who cultivated the plant; the first Europeans to do this were Jesuit missionaries, who spread the drinking habit as far as Ecuador.

When the yerba is harvested, the branches are dried sometimes with a wood fire, imparting a smoky flavour. Then the leaves and sometimes the twigs are broken up.

There are many brands and types of yerba, with twigs, and without and low powder content. Some types are less strong in flavor (suave, "soft") and there are blends flavored with mint, orange and grapefruit skin, etc.

Chemical composition and properties

Mate contains xanthines, which are alkaloids in the same family as caffeine, theophylline, and theobromine, well-known stimulants also found in coffee and chocolate. Mate also contains the chemical elements potassium, magnesium and manganese. Caffeine content varies between 0.3% and 1.7% of dry weight (compare this to 2.5–4.5% for tea leaves, and 1.5% for ground coffee).

Mate products are sometimes marketed as "caffeine-free" alternatives to coffee and tea, and said to have fewer negative effects. This is often based on a claim that the primary active xanthine in mate is "mateine", erroneously said to be a stereoisomer of caffeine (as it is not chemically possible for caffeine to have a stereoisomer). "Mateine" is an official synonym of caffeine in the chemical databases.

Researchers at Florida International University in Miami have found that yerba mate does contain caffeine, but some people seem to tolerate a mate drink better than coffee or tea. This is expected since mate contains different chemicals (other than caffeine) from tea or coffee.

From reports of personal experience with mate, its physiological effects are similar to (yet distinct from) more widespread caffeinated beverages like coffee, tea, or guarana drinks. Users report a mental state of wakefulness, focus and alertness reminiscent of most stimulants, but often remark on mate's unique lack of the negative effects typically created by other such compounds, such as anxiety, diarrhoea, "jitteriness", and heart palpitations.

Reasons for mate's unique physiological attributes are beginning to emerge in scientific research. Studies of mate, though very limited, have shown preliminary evidence that the mate xanthine cocktail is different from other plants containing caffeine most significantly in its effects on muscle tissue, as opposed to those on the central nervous system, which are similar to those of other natural stimulants. Mate has been shown to have a relaxing effect on smooth muscle tissue, and a stimulating effect on myocardial (heart) tissue.

Mate's negative effects are anecdotally claimed to be of a lesser degree than those of caffeine, though no explanation for this is offered or even credibly postulated, except for its potential as a placebo effect. Many users report that drinking yerba mate does not prevent them from being able to fall asleep, as is often the case with some more common stimulating

beverages, while still enhancing their energy and ability to remain awake at will. However, the net amount of caffeine in one preparation of yerba mate is typically quite high, in large part because the repeated filling of the mate with hot water is able to extract the highly-soluble xanthines extremely effectively. It is for this reason that one mate may be shared among several people and yet produce the desired stimulating effect in all of them.

In-vivo and in-vitro studies are showing yerba mate to exhibit significant cancer-fighting activity. Researchers at the University of Illinois (2005) found yerba mate to be "rich in phenolic constituents" and to "inhibit oral cancer cell proliferation".

An August 11, 2005 United States patent application (document #20050176777 & #20030185908 & #20020054926) cites yerba mate extract as an inhibitor of MAO activity; the maximal inhibition observed in vitro was 40–50%. A monoamine oxidase inhibitor is a type of antidepressant, so there is some data to suggest that yerba mate has calming effect in this regard.

Medicinal plants

Herbalism, also known as *Herbal medicine* and *phytotherapy*, is a folk and traditional medicinal practice based on the use of plants and plant extracts.

Finding healing powers in plants is an ancient idea. People in all continents have long used hundreds, if not thousands, of indigenous plants for treatment of various ailments dating back to prehistory. These plants are still widely used in ethnomedicine around the world.

The first generally accepted use of plants as healing agents were depicted in the cave paintings discovered in the Lascaux caves in France, which have been Radiocarbon dated to between 13,000 - 25,000 BCE.

Anthropologists theorize that over time, and with trial and error, a small base of knowledge would have been acquired within early tribal communities. As this knowledge base expanded over the generations, the specialized role of the shaman emerged. The process would likely have occurred in varying manners within a wide diversity of cultures.

Plants have an almost limitless ability to synthesize aromatic substances, most of which are phenols or their oxygen-substituted derivatives such as tannins. Most are secondary metabolites, of which at least 12,000 have been isolated, a number estimated to be less than 10% of the total. In many cases, these substances (esp. alkaloids) serve as plant defense mechanisms against predation by microorganisms, insects, and herbivores. Many of the herbs and spices used by humans to season food yield useful medicinal compounds.

The use of and search for drugs and dietary supplements derived from plants have accelerated in recent years. Pharmacologists, microbiologists, botanists, and natural-products chemists are combing the Earth for phytochemicals and leads that could be developed for treatment of various diseases. In fact, many modern drugs have been derived from plants.

The use of herbs to treat disease is almost universal among non-industrialized societies. A number of traditions came to dominate the practice of herbal medicine in the Western world at the end of the twentieth century:

- The Western, based on Greek and Roman sources,

The Ayurvedic from India, and

Chinese herbal medicine (Chinese herbology).

Many of the pharmaceuticals currently available to Western physicians have a long history of use as herbal remedies, including opium, aspirin, digitalis, and quinine.

Biological background

All plants produce chemical compounds as part of their normal metabolic activities. These can be split into primary metabolites, such as sugars and fats, found in all plants, and secondary metabolites found in a smaller range of plants, some only in a particular genus or species.

The autologous functions of secondary metabolites are varied. For example, as toxins to deter predation, or to attract insects for pollination. It is these secondary metabolites which can have therapeutic actions in humans and which can be refined to produce drugs. Some examples are inulin from the roots of dahlias, quinine from the cinchona, morphine and codeine from the poppy, and digoxin from the foxglove.

As of 2004, the National Center for Complementary and Alternative Medicine started to fund clinical trials into the effectiveness of herbal medicine.[1]

Surveys of a scientific approach to herbal medicine can be found in the books Evidence-based herbal medicine,[2] and Herbal and traditional medicine: molecular aspects of health.[3]

Popularity

A survey released in May 2004[4] by the National Center for Complementary and Alternative Medicine focused on who used complementary and alternative medicines (CAM), what was used, and why it was used. The survey was limited to adults age 18 years and over during 2002 living in the United States. According to this recent survey, herbal therapy, or use of natural products other than vitamins and minerals, was the most commonly used CAM therapy (18.9%)[5] when all use of prayer was excluded.

Herbal remedies are most common in Europe. In Germany, the term apothecary (Apotheke) is still used, and next to prescription drugs one can order essential oils, herbal extracts, or herbal teas. It is even seen as a preferred treatment over the unnecessary overuse of industrialized production of chemical medication.

Types of herbal medicine

Medicinal plants can be used by anyone, for example as part of a salad, an herbal tea or supplement, although some herbs considered dangerous are restricted from sale to the public. Sometimes such herbs are provided to professional herbalists by specialist companies. Many herbalists, both professional and amateur, often grow or wildcraft their own herbs. Many common weeds have medicinal properties (e.g. dandelion)

Medicinal herbs can be used in various forms:

Herbal teas

There are two methods of making herbal teas, infusion and decoction. Infusion is steeping lighter parts of the plant (leaves, flowers, light stems) in boiled water for several minutes. Decoction is boiling tougher parts, such as roots or bark for a longer period of time. Herbal teas are often used as a home remedy, and as an alternative to tea and coffee.

Herbal tinctures

Steeping a medicinal plant in alcohol extracts the alcohol-soluble principles into a liquid form that can be stored for long periods. Herbalists may mix several herbal tinctures to form an individualized prescription for each patient. Plant tinctures are also the basis for many homeopathic medicines.

Fluid extracts

Fluid extracts are stronger than herbal tinctures, and can be made with alcohol or glycerin.

Herbal poultices

Poultices are a solid, vegetable fat based mixture used externally. They have the shortest life span of any herbal remedy and must be made fresh for every use.

Powdered herbs and tablets

Herbs that are dried and (sometimes) certain parts are separated out then diced to powder fine consistency. Powered matter can then be compressed or put in an empty pill coating to form a tablet

Herbal creams and ointments

An ointment usually is mixed with beeswax (or something similar) to make it more applicable to outside the body, such as on a cut or scrape.

Essential oils

Main articles: Essential oil

Extraction of volatile liquid plant materials and other aromatic compounds from plants gives essential oils. These plant oils may be used internally in some forms of herbal medicine as well as in aromatherapy and generally for their perfume, although their medicinal use as

a natural treatment (alternative medicine) has proved highly efficacious in the treatment of headache and muscle pain[6], joint pain[7] and certain skin diseases[8]

Herbal supplements

Herbal supplements tend to be commercial products in tablet or capsule form manufactured and marketed by the health food industry for sale in retail outlets to the general public, although there are some types that are sold only to healthcare practitioners for prescription. Herbal supplements are often standardized to contain stated levels of active phytochemicals. Some herbalists may not agree with the standardization of active ingredients, preferring instead to use the whole plant.

Examples of herbal medicine

There are hundreds of herbal remedies. An experienced practitioner can offer a comprehensive holistic approach to health. Examples of some commonly used herbal medicines:

- Artichoke and several other plants reduced total serum cholesterol levels in preliminary studies.[9]
- Black cohosh and other plants that contain phytoestrogens (plant molecules with estrogen activity) have some benefits for treatment of symptoms resulting from menopause.[10]
- Echinacea extracts limit the length of colds in some clinical trials, although some studies have found it to have no effect.[11]
- Garlic lowers total cholesterol levels, mildly reduces blood pressure, reduces platelet aggregation, and has antibacterial properties.[12]
- Grapefruit seed extract as a natural antimicrobial has minimal effectiveness as an anti-bacterial, anti-parasitic, and anti-fungal herb.[13][14][15][16][17]
- Nigella sativa (Black cumin) is a general medicinal plant used for diverse ailments such as cough, pulmonary infections, asthma, influenza, allergy, hypertension and stomach ache. The seeds are considered carminative, stimulant, diuretic and galactogogue. It is often taken with honey. Seed powder or oil is externally applied for eruptions of skin.
- Peppermint tea for problems with the digestive tract, including irritable bowel syndrome and nausea.
- Rauvolfia Serpentina, used extensively in India for sleeplessness, anxiety, and high blood pressure. The first proven allopathic medicine for high blood pressure was extracted from this herb.
- St John's wort, has yielded positive results, proving more effective than a placebo for the treatment of mild to moderate depression in some clinical trials.[18]
- Valerian root can be used to treat insomnia.

Dangers

A common misconception about herbalism and the use of 'natural' products in general, is that 'natural' equals safe. However many plants have chemical defence mechanisms against predators that can have adverse or lethal effects on humans. Examples are poison hemlock and nightshade, which can be deadly. Herbs can also have undesirable side-effects just as pharmaceutical products can. These problems are exacerbated by lack of control over dosage and purity. Furthermore, if given in conjunction with drugs, there is danger of 'summation', where the herb and the drug have similar actions and add together to make an 'overdose'. In animals, there are other dangers. There may be residues in food from farm animals (e.g. eggs, milk, meat) or danger of 'doping' in competition animals. The latter may also apply to human athletes.

Effectiveness

As noted above, there have been scientific studies which show that certain plant products can cure or prevent certain diseases, and these products or pharmaceutical drugs derived from them are patented by pharmaceutical companies and sold for high profit in modern Western medicine. Pharmaceutical firms argue that the individual should not have control over their health to the point of experimenting with "potentially hazardous materials".

Most herbal traditions have accumulated knowledge without modern scientific controls to distinguish between the placebo effect, the body's natural ability to heal itself, and the actual benefits of the herbs themselves. This is because most knowledge also pre-dates modern discoveries in human physiology and biochemistry. In fact, much knowledge dates back to medieval Europe, and was exterminated along with the witches during the burnings. Together the church and male-dominated 19th and 20th century medicine discredited much of this knowledge, and most has been lost.

There is a danger that herbal remedies will be used in place of other medical treatments which have been scientifically proven to be safe and effective, resulting in the development or worsening of a medical condition which could have been better prevented or treated. There is also a danger that an herbal remedy may itself cause harm which is unanticipated due to a lack of a full understanding of its composition and biochemical effects.

Name confusion

The common names of herbs (folk taxonomy) may not reflect differences in scientific taxonomy, and the same (or a very similar) common name might group together different plant species with different effects. For example, in 1993 in Belgium, in a TCM remedy for weight loss, one herb (Stephania tetrandra) was swapped for another (Aristolochia fangchi) whose name in Chinese was extremely similar but which contained higher levels of a renal toxin, aristolochic acid; this quid pro quo resulted in 105 cases of kidney damage. [19][20]

Standards and quality control

The legal status of herbal ingredients varies by country. For example, Ayurvedic herbal products may contain levels of heavy metals that are considered unsafe in the U.S., but heavy metals are considered therapeutic in Ayurvedic medicine.

In the United States, most herbal remedies are regulated as dietary supplements. Many herbs for home use can be grown in a small home garden too.

Medical interaction

In consultation with a physician, usage of herbal remedies should be clarified, as some herbal remedies have the potential to cause adverse drug interactions when used in combination with various prescription and over-the-counter pharmaceuticals. Dangerously low blood pressure may result from the combination of an herbal remedy that lowers blood pressure together with prescription medicine that has the same effect. In particular, many herbs should be avoided during pregnancy.[21] However, most herbal books alert the reader to necessary precautions.

Not all physicians may be familiar with the effects of different types of herbal medicine, but general practitioners should be able to refer patients to a specialist, or investigate the medical literature on their behalf.

See also

- Chinese herbology

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List of medicinal herbs

Species - Common name (Properties)

Achillea millefolium - Yarrow (diaphoretic, astringent, tonic, stimulant, vulnerary)

***Allium sativum* - Garlic ()anti-microbial**

Anethum graveolens - Dill and Dill oil (carminative)

Artemisia absinthium L - Wormwood (tonic, stomachic, febrifuge, anti-parasitic)

Artemisia annua L. - Sweet sagewort

Arum Maculatum - Lords and Ladies (vulnerary - leaf used externally to draw out abcesses.)

Crataegus spp. - Hawthorn

Digitalis purpurea - Foxglove

Echinacea purpurea - Purple coneflower, and other species of Echinacea

Glycyrrhiza glabra - Liquorice

Hydrastis canadensis - Goldenseal

Hypericum perforatum - St. John's Wort

Marrubium vulgare - Horehound

Matricaria recutita (Chamomilla recutita) - Chamomile

Nepeta cataria - Catnip

Passiflora spp. - Passion-flower

Plantago spp. - Plantain and Psyllium

Salvia Stenophylla - Blue Mountain Sage

Symphytum officinale - Comfrey

Tanacetum parthenium (Chrysanthemum parthenium) - Feverfew

Taraxacum officinale - Dandelion

Tilia spp. - Lime Blossom

Urtica dioica - Urtica dioica

Valeriana officinalis - Valerian

See also

- Herbalism

Bay Laurel

Scientific classification

Kingdom: Plantae
Division: Magnoliophyta
Class: Magnoliopsida
Order: Laurales
Family: Lauraceae
Genus: Laurus
Species: *L. nobilis*
Binomial name *Laurus nobilis*

The *Bay Laurel* (Laurus nobilis, Lauraceae), also known as *True Laurel*, *Sweet Bay*, *Grecian Laurel*, *Laurel*, or *Bay Tree*, is an aromatic evergreen tree or large shrub reaching 10–18 m tall, native to the Mediterranean region.

The leaves are 6–12 cm long and 2–4 cm broad, with a characteristic finely serrated and wrinkled margin. It is dioecious, with male and female flowers on separate plants; each flower is pale yellow-green, about 1 cm diameter, borne in pairs together beside a leaf. The fruit is a small black berry about 1 cm long, containing a single seed.

Uses and symbolism

Bay Laurel is the source of the bay leaves which are used for their flavour in cooking. It was also the source of the laurel wreath of ancient Greece, and therefore the expression of "resting on one's laurels". A wreath of bay laurels was given as the prize at the Pythian Games. In the Bible, the sweet-bay is often an emblem of prosperity and fame. It is also the

source of the word baccalaureate (laurel berry), and of poet laureate and indeed the qualification used as an equivalent to the English A-Level.

Some evidence from the medical literature supports Bay Laurel having these uses:

- **Antioxidative:** Fitoterapia. 2003 Sep;74(6):613-6.
  - Analgesic and anti-inflammatory: Phytother Res. 2003 Aug;17(7):733-6.
  - Anticonvulsant (antiepileptic): Phytomedicine. 2002 Apr;9(3):212-6.

It is also widely cultivated as an ornamental plant in regions with mediterranean or oceanic climates, and as an indoor plant in colder regions.

Trivia

Bay laurel leaves are used in the design of the 10 yen coin in Japan.

In Greek mythology, the tree was first formed when the nymph Daphne changed into it to escape the pursing Olympian God Apollo.

Cardamom

Scientific classification

Kingdom: Plantae
Division: Magnoliophyta
Class: Liliopsida
Order: Zingiberales
Family: *Zingiberaceae*

Genera

Aframomum
Amomum
Elettaria

The name *cardamom* (sometimes written *cardamon*) is used for species within three genera of the ginger family Zingiberaceae, namely Elettaria, Amomum and Aframomum.

Types of cardamom and their distribution

The three main genera of the ginger family that are named as forms of cardamom are distributed as follows:

- *Elettaria* (commonly called cardamom, green cardamom, or true cardamom) is distributed from India to Malaysia.

- *Amomum* (commonly known as black cardamom, Kravan, Java cardamom, Bengal cardamom, Siamese cardamom, white or red cardamom) is distributed mainly in Asia and Australia.
- *Aframomum* (Madagascar cardamom, grains of paradise) is distributed in mainland Africa and Madagascar.

Uses

All the different cardamom species and varieties are used mainly as cooking spices and as medicines. In general,

- Elettaria subulatum (the usual type of cardamom) is used as a spice, a masticatory, and in medicine; it is also sometimes smoked; it is used as a food plant by the larva of the moth Endoclita hosei.
- Aframomum is used as a spice (see Grains of Paradise);
- Amomum is used as an ingredient in traditional systems of medicine in China, India, Korea, and Vietnam.
- Can be used as a traditional flavouring to Turkish coffee.

Uses in cuisines around the world

Cardamom has a strong, unique taste, with an intensely aromatic fragrance. It is often used in baking in Scandinavia. One of the most expensive spices by weight, little is needed to impart the flavour. Cardamom is best stored in pod form, because once the seeds are exposed or ground, they quickly lose their flavour. However, high-quality ground cardamom is often more readily (and cheaply) available, and is an acceptable substitute. For recipes requiring whole cardamom pods, a generally accepted equivalent is 10 pods equals 1½ teaspoons of ground cardamom.

In traditional medicine

In India, green cardamom (A. subulatum) is broadly used to treat infections in teeth and gums, to prevent and treat throat troubles, congestion of the lungs and pulmonary tuberculosis, inflammation of eyelids and also digestive disorders. It is also reportedly used as an antidote for both snake and scorpion venom.

Species in the genus Amomum is also used in traditional Indian medicine. Among other species, varieties and cultivars, Amomum villosum is used in traditional Chinese medicine to treat stomach-aches, constipation, dysentery, and other digestion problems. "Tsaoko" cardamom is cultivated in Yunnan, China, both for medicinal purposes and as a spice.

Liquorice

Scientific classification

Kingdom: Plantae
Division: Magnoliophyta
Class: Magnoliopsida
Order: Fabales
Family: Fabaceae
Subfamily: Faboideae

Tribe: Galegeae
Genus: Glycyrrhiza
Species: *G. glabra*

Binomial name Glycyrrhiza glabra

Liquorice or *licorice* (pronounced IPA: ['ljkY€zjƒ]) is the root of Glycyrrhiza glabra, from which a sweet flavour can be extracted. The liquorice plant is a legume (related to beans and peas) and native to southern Europe and parts of Asia. It is a herbaceous perennial, growing to 1 metre in height, with pinnate leaves about 7–15 centimetres (3–6 inches) long, with 9–17 leaflets. The flowers are 0.8–1.2 cm (1/3 to 1/2 inch) long, purple to pale whitish blue, produced in a loose inflorescence. The fruit is an oblong pod, 2–3 centimetres (about 1 inch) long, containing several seeds.

Cultivation and uses

Liquorice is grown as a root crop mainly in southern Europe. Very little commercial liquorice is grown in North America, where it is replaced by a related native species, American Licorice (G. lepidota), which has similar uses.

Liquorice extract is produced by boiling liquorice root and subsequently evaporating most of the water (in fact, the word 'liquorice' is derived from the Ancient Greek words for 'sweet root'). Liquorice extract is traded both in solid and syrup form. Its active principle is glycyrrhizin, a sweetener more than 50 times as sweet as sucrose which also has pharmaceutical effects. The related Chinese Liquorice (G. uralensis), which is used extensively in traditional Chinese medicine, contains this chemical in much greater concentration.

Culinary use

Liquorice flavour is found in a wide variety of liquorice candies. The most popular in the United Kingdom are very sweet Liquorice Allsorts. In continental Europe, however, far stronger, saltier candies are preferred. It should be noted, though, that in most of these candies the taste is reinforced by aniseed oil, and the actual content of liquorice is quite low. Additionally, liquorice is found in some soft drinks (such as root beer), and is in some herbal teas where it provides a sweet aftertaste. The flavour is common in medicines to disguise unpleasant flavours.

Liquorice is popular in Italy, particularly in the South, in its natural form. The root of the plant is simply dug up, washed and chewed as mouth-freshener. Throughout Italy unsweetened liquorice is consumed in the form of small black pieces made only from 100% pure liquorice extract; the taste is bitter and intense.

In Britain and The Netherlands in the past dried liquorice root was chewed as a sweet by youngsters.

Chinese cuisine uses liquorice as a culinary spice for savoury foods. It is often employed to flavour broths and foods simmered in soy sauce.

Other herbs and spices of similar flavour include Anise, star anise, tarragon, and fennel.

Medicinal use

Powdered liquorice root is an effective cough remedy (expectorant), and has been used for this purpose since ancient times, especially in ayurvedic medicine where it is also used in tooth powders. Modern cough syrups often include liquorice extract as an ingredient. Additionally, licorice may be useful for both mouth ulcers and peptic ulcers. Naturopathic medicinal uses include treatment of peptic and oral ulcers.

Liquorice is also a mild laxative. Large doses of glycyrrhizinic acid and glycyrrhetinic acid in liquorice extract can lead to hypokalemia and serious increases in blood pressure, a syndrome known as apparent mineralocorticoid excess. These side effects stem from the inhibition of the enzyme 11^2-hydroxysteroid dehydrogenase (type 2) and subsequent increase in activity of cortisol on the kidney. 11^2-hydroxysteroid dehydrogenase normally inactivates cortisol in the kidney; thus, licorice's inactivation of this enzyme makes the concentration of cortisol appear to increase. Cortisol acts at the same receptor as the hormone aldosterone in the kidney; thus, the effects mimic aldosterone excess, although aldosterone remains low or normal during licorice overdose. Cortisol does not actually increase either; however, its activity in the kidney effectively increases due to the disabling of this enzyme. To decrease the chances of these serious side effects, deglycyrrhizinated licorice (DGL) preparations are available.

Licorice affects the body's endocrine system. It can lower the amount of serum testosterone, but whether it affects the amount of free testosterone is unclear. A PubMed search for *licorice AND testosterone* will provide additional information.

The disabling of similar enzymes in the gut by glycyrrhizinic acid and glycyrrhetinic acid also causes increased mucus and decreased acid secretion. Thus, licorice may in moderate amounts soothe an upset stomach and is used as an aid for healing stomach ulcers.

Recently, a study is being conducted by clinical psychologist Hunna Watson into the therapeutic potential of liquorice on people with mood disorders.

Papaya

Scientific classification

Kingdom: Plantae
Division: Magnoliophyta
Class: Magnoliopsida
Order: Brassicales
Family: Caricaceae
Genus: Carica
Species: *C. papaya*

Binomial name *Carica papaya*

The *papaya*, also known as *mamão*, *tree melon*, *fruta bomba*, *lechosa* (Venezuela, Puerto Rico, and the Dominican Republic), or *pawpaw* is the fruit of the tree Carica papaya, in the genus Carica.

It is a small unbranched tree, the single stem growing to 5-10 m tall, with the spirally arranged leaves confined to the top of the trunk; the lower trunk is conspicuously scarred with the leaf scars of where older leaves and fruit were borne. The leaves are large, 50-70 cm diameter, deeply palmately lobed with 7 lobes. The flowers are produced in the axils of the leaves, maturing into the large 15-45 cm long, 10-30 cm diameter fruit. The fruit is ripe when it feels soft (like a ripe avocado or a bit softer) and its skin has attained an amber to orange hue.

Cultivation and uses

Originally from southern Mexico, Central America and northern South America, the papaya is now cultivated in most countries with a tropical climate like India and the Philippines.

The primary use of the papaya is as an edible fruit. It is usually eaten raw, without the skin or seeds. The unripe green fruit of papaya can be eaten cooked usually in curries, salads and stews.

Papaya is rich in an enzyme called papain (a protease which is useful in tenderizing meat) and other proteins. Its utility is in breaking down the tough meat fibers and it has been utilized for thousands of years in its native South America. It is included as a component in powdered meat tenderizers. Papaya enzyme is also marketed in tablet form to remedy digestive problems. Caution should be taken when harvesting, as papaya is known to release a latex fluid when not quite ripe, which can cause irritation and provoke allergic reaction in some people. The papaya fruit and leaves also contains carpaine, an anthelmintic alkaloid which could be dangerous in high doses.

Women in India and Sri Lanka and other parts of the world have long used papaya as a folk remedy for contraception and abortion. Medical research in animals has confirmed the contraceptive and abortifacient capability of papaya, and also found that papaya has contraceptive effects in men as well. Unripe papaya is especially effective, in large amounts or high doses. Papaya is not teratogenic and will not cause miscarriage in small, ripe amounts. Phytochemicals in papaya may suppress the effects of Progesterone. [1]

The black seeds are edible, and have a sharp, spicy taste. They are sometimes ground up and used as a substitute for black pepper. In some parts of Asia the young leaves of papaya are steamed and eaten like spinach.

Excessive consumption of papaya, like of carrots, can cause carotenemia, the yellowing of soles and palms which is otherwise harmless.

See also

- Papaya Coconut, a 1986 hit song by Swedish pop and country singer Kikki Danielsson.

Castor oil plant

Scientific classification

Kingdom: Plantae
Division: Magnoliophyta
Class: Magnoliopsida
Order: Malpighiales
Family: Euphorbiaceae
Subfamily: Acalyphoideae
Tribe: Acalypheae
Subtribe: *Ricininae*
Genus: *Ricinus*
Species: *R. communis*

Binomial name Ricinus communis

The *Weed plant* (Ricinus communis) is a plant species of the Euphorbiaceae and the sole member of the genus *Ricinus* and of the subtribe *Ricininae*. It is the origin of the *castor bean* which, despite its name, is not a true bean. The name Ricinus is a Latin word for tick; the seed is so named because it has markings and a bump at the end which resemble certain ticks. It is the source of castor oil, which has a wide variety of uses, and ricin, a poison (the ricin from 1-2 seeds can kill an adult).

Although castor is probably indigenous to Eastern Africa, today castor is distributed worldwide. Castor establishes itself easily as a "native" plant and can often be found on wasteland, near railroads and has recently also been used extensively as decorative plant in parks and other public areas.

Castor seeds have been found in Egyptian tombs dating back to 4000 BC. Herodotus and other Greek travellers have noted the use of castor seed oil for lighting and body anointments.

The use of castor seed oil in India has been documented since 2000 BC for use in lamps and in local medicine as a laxative. Castor seed and its oil have also been used in China for centuries, mainly prescribed in local medicine for internal use or use in dressings.

Although monotypic, the castor plant can vary greatly in its growth habit and appearance. Some castor plants are perennials which can take weed the size of small trees, and other plants are dwarf types and are grown as annuals. There also exists an enormous variation in leaf shape and colouring which has led to a selection by breeders for use as ornamental plants. Castor is used as a food plant by the larvae of some Lepidoptera species including Giant Leopard Moth, Hypercompe hambletoni and The Nutmeg.

Scanning electron microscope image

Castor seed contains between 40% and 60% oil that is rich in triglycerides, mainly ricinolein.

Global castor seed production is around 1 million tons per year. Leading producing areas are India, China and Brazil. There are several active breeding programmes.

Dandelion

Scientific classification

Kingdom: Plantae
Division: Magnoliophyta
Class: Magnoliopsida
Order: Asterales
Family: Asteraceae
Genus: *Taraxacum*

A *dandelion* is a short plant, usually with a yellow flower head and notched leaves. A dandelion flower head consists of many tiny flowers. The dandelion is native to Europe and Asia, and has spread to many other places. The dandelion is also known by its generic name Taraxacum. In Northern areas and places where the dandelion is not native, it reproduces asexually.

Detailed Description

Dandelion (*Taraxacum*) is a large genus of flowering plants in the family Asteraceae. They are tap-rooted biennial or perennial herbaceous plants, native to temperate areas of the Northern Hemisphere of the Old World.

The genus is taxonomically very complex, with numerous macrospecies, and polyploidy is also common; over 250 species have been recorded in the British Isles alone (Richards 1972). Some botanists take a much narrower viewpoint, and only accept a total of about 60 species.

The leaves are 5-25 cm long, simple and basal, entire or lobed, forming a rosette above the central taproot. As the leaves grow outward they push down the surrounding vegetation, such as grass in a lawn, killing the vegetation by cutting off the sunlight. A bright yellow flower head (which is open in the daytime but closes at night) is borne singly on a hollow stem (scape) which rises 4-30 cm above the leaves and exudes a milky sap (latex) when broken. A rosette may produce several flowering stems at a time. The flower head is 2-5 cm in diameter and consists entirely of ray florets.

Dandelions are used as food plants by the larvae of some species of Lepidoptera. [1]

Away from their native regions, they have become established in the Americas, Australia and New Zealand as weeds. They are now common plants throughout all temperate regions.

The Dandelion Clock

The flower matures into a globe of fine filaments that are usually distributed by wind, carrying away the seed-containing achenes. This globe (receptacle) is called the "dandelion clock", and blowing it apart is a popular pastime for children. In German it's called a Pusteblume, translated as "blow flower". The number of blows required to completely rid the clock of its seeds is deemed to be the time of day.

The Seeds

The flower head is surrounded by bracts (sometimes mistakenly called sepals) in two series. The inner bracts are erect until the seeds mature, then flex down to allow the seeds to disperse; the outer bracts are always reflexed downward. Some species drop the "parachute" (called a pappus, modified sepals) from the achenes. Between the pappus and the achene, there is a stalk called beak, which elongates as the fruit matures. The beak breaks off from the achene quite easily.

Name

The name dandelion is derived from the Old French, dent-de-lion, which is literally "lion's tooth", referring to the sharply-lobed leaves of the plant. The English spelling reflects the French pronunciation at the time this French word was absorbed into English. The first written usage of the word occurs in an "herbal" dated 1373, but there is a 1363 document in which the word "dandelion" was used as a proper name (Willelmus Dawndelyon).

In German, the dandelion is called Löwenzahn, which is also translated as "lion's tooth." In modern French the plant is called pissenlit, which means "urinate in bed", apparently referring to its diuretic properties. Likewise, "pissabeds" is an English folkname for this plant, and "piscialletto" is one of its folknames in Italian (with "dente di leone", meaning "lion's tooth"). Similarly in Spanish, it is known as the "meacamas", but also commonly "diente de león".

Selected species

- Taraxacum officinale (syn. T. vulgare), Common Dandelion. Found in many forms, but differs at least from the following species:
 Taraxacum albidum, a white-flowering Japanese dandelion.
 Taraxacum japonicum, Japanese dandelion. No ring of smallish, downward-turned leaves under the flowerhead.
 Taraxacum laevigatum (syn. T. erythrospermum), Red-seeded Dandelion; achenes reddish brown and leaves deeply cut throughout length. Inner bracts' tips are hooded.

Seed development and genetics

As aforementioned, the taxonomical situation of the genus is quite complex, mainly because many dandelions are genetically triploid. An odd number of chromosomes usually is associated with sterility, but dandelions with this karyotype can reproduce without fertilization, a process called apomixis[2]. In these individuals flowers are useless vestigial structures, although they may still produce a small percentage of fertile pollen, keeping some genetic contact with sexual individuals. Diploid dandelions develop seeds after cross-pollination and are self-incompatible. In most zones of southern Europe and Asia, dandelion populations are sexual or mixed sexual-apomictic, while in northern countries only triploid and tetraploid apomicts are present, as is in the zones where it is not native. This seems to be linked to higher temperatures, survival of pre-glacial populations and human impact, but the subject is still being studied.

There are usually 54 to 172 seeds produced per head, but a single plant can produce more than 2000 seeds a year. It has been estimated that more than 97 000 000 seeds/hectare could be produced every year by a dense stand of dandelions.

Uses

While the dandelion is considered a weed by many gardeners, the plant does have several culinary and medicinal uses. Dandelions are grown commercially at a small scale as a leaf vegetable. The plant can be eaten cooked or raw in various forms, such as in soup or salad. They are probably closest in character to mustard greens. Usually the young leaves and unopened buds are eaten raw in salads, while older leaves are cooked. Raw leaves have a slightly bitter taste. Dandelion salad is often accompanied with hard boiled eggs. The leaves are high in vitamin A, vitamin C and iron, carrying more iron and calcium than spinach.[3]

Dandelion flowers can be used to make dandelion wine. The recipe usually contains citrus fruit. Another recipe using the plant is dandelion flower jam. Ground roasted dandelion root can be used as a coffee substitute. Drunk before meals, it is believed to stimulate digestive functions. Sold in most health food stores, often in a mixture, it is considered an excellent cleansing tonic for the liver.

Dandelion root is a registered drug in Canada, sold as a diuretic. A leaf decoction can be drunk to "purify the blood", for the treatment of anemia, jaundice, and also for nervousness. The milky latex has been used as a mosquito repellent; the milk is also applied to warts, helping get rid of them without damaging the surrounding skin. A dye can also be obtained from the roots of the plant. A new mixture of roasted roots is sold as a product called DandyBlend which tastes like coffee after the inulin in the dandelion is roasted.

"Dandelion and Burdock" is a soft drink that has long been popular in the United Kingdom with authentic recipes are sold by health food shops, but it is not clear whether the cheaper supermarket versions actually contain either plant.

This plant also is useful in farming, because its deep, strong roots break up hardpan.

Antioxidant Properties of Dandelion

Dandelion contains Luteolin, an antioxidant, and has demonstrated antioxidant properties without cytotoxicity.

Chun Hu and David D. Kitts. Food, Nutrition and Health, Faculty of Agricultural Sciences, University of British Columbia, Vancouver, BC, Canada. October 2004. Luteolin and luteolin-7-O-glucoside from dandelion flower suppress iNOS and COX-2 in RAW264.7 cells. Springer Netherlands. *245*:1-2(107-113).

Caffeic Acid and Carcinogenicity

Caffeic acid is a secondary plant metabolite produced in dandelion, yarrow, horsetail and whitethorn. Despite its name, it is totally unrelated to caffeine. Recent studies have revealed this acid may be carcinogenic. Caffeic acid was tested for carcinogenicity by oral administration in mice, it produced renal cell adenomas in females, and a high incidence of renal tubular cell hyperplasia in animals of each sex.[4]

False Dandelions

Dandelions are so similar to catsears (Hypochoeris) that catsears are also known as "false dandelions". Both plants carry similar flowers which form into windborne seeds. However, catsear flowering stems are forked and solid, whereas dandelions possess unforked stems that are hollow. Both plants have a rosette of leaves and a central taproot. However, the leaves of dandelions are jagged in appearance, whereas those of catsear are more lobe-shaped and hairy.

Other plants with similar flowers include hawkweeds (Hieracium) and hawksbeards (Crepis). These are both readily distinguished by their branched flowering stems.

References and external links

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2. ^ http://www.talkorigins.org/faqs/comdesc/section2.html#vestiges

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4. ^ Caffeic acid phenethyl ester is a potent and specific inhibitor of activation of nuclear transcription factor NF-kappa B., Natarajan K, Singh S, Burke TR Jr, Grunberger D, Aggarwal BB., Proc. Natl. Acad. Sci. U S A., 1996 Aug 20;93(17):9090-5.

Echinacea

Scientific classification

Kingdom: Plantae
Division: Magnoliophyta
Class: Magnoliopsida
Order: Asterales
Family: Asteraceae
Tribe: Heliantheae
Genus: *Echinacea*

Echinacea is a genus of nine species of flowering plants in the Family Asteraceae, all native to eastern North America.

The genus name is from the Greek echino, meaning "spiny", due to the spiny central disk. They are herbaceous, drought-tolerant perennial plants growing to 1 or 2 m in height. The leaves are lanceolate to elliptic, 10-20 cm long and 1.5-10 cm broad. Like all Asteraceae, the flowers are a composite inflorescence, with purple (rarely yellow or white) florets arranged in a prominent, somewhat cone-shaped head; "cone-shaped" because the petals of the outer ray florets tend to point downward (are reflexed) once the flower head opens, thus forming a cone.

The species of Echinacea are:

- Echinacea angustifolia - Narrow-leaf Coneflower
Echinacea atrorubens - Topeka Purple Coneflower
Echinacea laevigata - Smooth Coneflower, Smooth Purple Coneflower
Echinacea pallida - Pale Purple Coneflower
Echinacea paradoxa - Yellow Coneflower, Bush's Purple Coneflower
Echinacea purpurea - Purple Coneflower, Eastern Purple Coneflower
Echinacea sanguinea - Sanguin Purple Coneflower
Echinacea simulata - Wavyleaf Purple Coneflower
Echinacea tennesseensis - Tennessee Coneflower

Uses

Some species of Echinacea, notably E. purpurea, E. angustifolia, and E. pallida, are grown as ornamental plants in gardens. It tolerates a wide variety of conditions, maintains attractive foliage throughout the season, and multiplies rapidly. Appropriate species are used in prairie restorations. Some species are used by domestic stock for forage; an abundance of these plants on rangeland supposedly indicates "good health".

Echinacea rhizome was used by North American Plains Indians, perhaps more than most other plants, for various herbal remedies. In the 1930's "Echinacea" became popular in both Europe and America as a herbal medicine. Echinacea has been attributed with the ability to boost the body's immune system and ward off infections, particularly the common cold. Depending on which species is used, herbal medicinals can be prepared from the above-

ground parts and/or the root. It is not known which of echinacea's many chemical components might be responsible for its touted health benefits, although all species possess compounds of a chemical class called phenols (as do most other plants). Cichoric and caftaric acids are phenols that are present in E. purpurea; echinacoside is a phenol found in higher levels within E. angustifolia and E. pallida roots. When making herbal remedies, these phenols can serve as markers to evaluate the quantity of echinacea in the product. Other constituents that may be important include alkamides and polysaccharides.

A medical study (Taylor et al. 2003[1].) demonstrated that echinacea products made from the entire plant (not just the root), and taken after the second cold symptom appeared, provided no measurable beneficial effect for children in treating the severity or duration of symptoms caused by the common cold virus. Studies by the University of Virginia School of Medicine (Turner, 2005 [2]) confirmed these results, and added that Echinacea had no clinically significant effects on the common cold even if taken immediately upon infection, or as a prophylaxis starting a week prior to symptoms of infection. However, a University of Maryland review of available studies concluded that Echinacea, when taken at first sign of a cold, reduced cold symptoms or shortened their duration. This conclusion was based on 13 European studies. The University of Maryland also found that three of four studies concluded that taking Echinacea to prevent a cold was ineffective. Echinacea may, however, be useful when treating Athlete's foot with Econazole, or in cancer treatment[3]

Echinacea herbals should not be taken by persons with progressive systemic and auto-immune disorders such as tuberculosis, leicosis, connective tissue disorders, collagenosis, and related diseases such as lupus erythematosus, according to the German Kommission E. Its use in AIDS or against opportunistic infections in AIDS patients is controversial: the Kommission E recommend against it, but this seems to be on theoretical rather than clinical grounds [4]. It should not be used with other known hepatotoxic drugs such as anabolic steroids, amiodarone (Pacerone® or Cordarone®), methotrexate, or ketoconazole (Nizoral®). [5].

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Eucalyptus

Scientific classification

Kingdom: Plantae
Division: Magnoliophyta
Class: Magnoliopsida
Order: Myrtales
Family: Myrtaceae
Genus: *Eucalyptus*

Species About 700

Eucalyptus is a diverse genus of trees (and a few shrubs), the members of which dominate the tree flora of Australia. There are more than 700 species of Eucalyptus, mostly native to Australia, with a very small number found in adjacent parts of New Guinea and Indonesia and one as far north as the Philippines. Eucalyptus can be found in almost every part of the Australian continent, adapted to all of its climatic conditions; in fact, no other continent is so characterised by a single genus of tree as Australia is by eucalyptus. Many, but far from all, are known as *gum trees*; other names for various species include *mallee*, *box*, *ironbark*, *stringybark*, and *ash*.

Description

Flowers and leaves

The most readily recognisable characteristics of Eucalyptus species are the distinctive flowers and fruits. The name Eucalyptus, from the Greek words eu-, well, and kaluptos, cover, meaning "well-covered", describes the bud cap (botanically called an operculum). This cap forms from modified petals and falls off as the flower opens. Thus flowers have no petals, decorating themselves instead with many showy stamens. The woody fruits, known as gumnuts, are roughly cone-shaped and have valves at the end which open to release the seeds.

Nearly all eucalypts are evergreen but some tropical species lose their leaves at the end of the dry season. As in other members of the Myrtle family, eucalypt leaves are covered with oil glands. The copious oils produced are an important feature of the genus. Eucalypts also exhibit leaf dimorphism. When young, their leaves are opposite, oval to roundish, and occasionally without a petiole. When one to a few years old, the leaves become alternate, lanceolate to falcate (sickle-shaped), quite slender and pendulous with longer petioles. The adult leaves of most species, as well as the juvenile leaves of some, are the same on both sides, lacking the distinction between upper and lower surfaces shown by the leaves of most plants. Most species do not flower until adult foliage starts to appear; E. cinerea and E. perriniana are notable exceptions.

Bark

The bark dies annually and species can be roughly grouped based on its appearance. In smooth-barked trees most of the bark is shed, leaving a smooth surface that is often colourfully mottled. With rough-barked trees the dead bark persists on the tree and dries out. Many trees, however, have smooth bark at the top but rough bark on the trunk or its bottom. The types of rough bark is often used to broadly label a group of eucalypts.

They are:

- *Stringybark* - consists of long-fibres and can be pulled off in long pieces. It is usually thick with a spongy texture.
- *Ironbark* - is hard, rough and deeply furrowed. It is soaked with dried kino (a sap exuded by the tree) which gives a dark red or even black colour.
- *Tessellated* - bark is broken up into many distinct flakes. They are corkish and can flake off.
- *Box* - has short fibres. Some also show tessellation.
- *Ribbon* - this has the bark coming off in long thin pieces but still loosely attached in some places. They can be long ribbons, firmer strips or twisted curls.

Related genera

A small genus of similar trees, Angophora, has also been known since the 18th century. In 1995 new evidence, largely genetic, indicated that some prominent eucalypt species were actually more closely related to Angophora than to the other eucalypts; they were split off into the new genus Corymbia. Although separate, the three groups are allied and it remains acceptable to refer to the members of all three genera Angophora, Corymbia and Eucalyptus as "eucalypts". The coolibah trees, referred to in Waltzing Matilda, are eucalypts E. coolabah and E. microtheca.

Tall timber

Today, specimens of the Australian Mountain Ash, Eucalyptus regnans, are among the tallest trees in the world at up to 92 metres in height [1] and the tallest of all flowering plants; taller trees such as the Coast Redwood are all conifers. There is credible evidence however that at the time of European settlement of Australia some Mountain Ash were indeed the tallest plants in the world.

Tolerance

Most eucalypts are not tolerant of frost, or only tolerate light frosts down to -3°C to -5°C; the hardiest, are the so-called Snow Gums such as Eucalyptus pauciflora which is capable of withstanding cold and frost down to about -20°C. Two sub-species, E. pauciflora niphophila and E. pauciflora debeuzevillei in particular are even hardier and can tolerate even quite severe continental type winters.

Several other species, especially from the high plateau and mountains of central Tasmania such as E. coccifera, E. subcrenulata, and E. gunnii have produced extreme cold hardy forms and it is seed procured from these genetically hardy strains that are planted for ornament in colder parts of the world.

Animal relationships

An essential oil extracted from eucalypt leaves contains compounds that are powerful natural disinfectants and which can be toxic in large quantities. Several marsupial herbivores, notably koalas and some possums, are relatively tolerant of it. The close correlation of these oils with other more potent toxins called formylated phloroglucinol compounds allows koalas and other marsupial species to make food choices based on the smell of the leaves. However, it is the formylated phloroglucinol compounds that are the most important factor in choice of leaves by koalas.

Eucalypts support the larvae of a number of Lepidoptera species.

Hazards

Eucalypts have a habit of dropping entire branches off as they grow. Eucalyptus forests are littered with dead branches. The Australian Ghost Gum Eucalyptus papuana is also termed the "widow maker", due to the high number of pioneer tree-felling workers who were killed by falling branches. Many deaths were actually caused by simply camping under them, as they shed whole and very large branches to conserve water during periods of drought. For this reason, one should never camp under an overhanging branch. This may be the real reason behind the drop bear story told to children - the idea is to keep them away from being under dangerous branches.

Fire

On warm days vapourised eucalyptus oil rises above the bush to create the characteristic distant blue haze of the Australian landscape. Eucalyptus oil is highly flammable (trees have been known to explode) and bush fires can travel easily through the oil-rich air of the tree crowns. The dead bark and fallen branches are also flammable. Eucalypts are well adapted for periodic fires, in fact most species are dependent on them for spread and regeneration, both from reserve buds under the bark, and from fire-germinated seeds sprouting in the ashes.

Eucalypts originated between 35 and 50 million years ago, not long after Australia-New Guinea separated from Gondwana, their rise coinciding with an increase in fossil charcoal deposits (suggesting that fire was a factor even then), but they remained a minor component of the Tertiary rainforest until about 20 million years ago when the gradual drying of the continent and depletion of soil nutrients led to the development of a more open forest type, predominantly Casuarina and Acacia species. With the arrival of the first humans about 50 thousand years ago, fires became much more frequent and the fire-loving eucalypts soon came to account for roughly 70% of Australian forest.

Eucalypts regenerate quickly after fire. After the Canberra bushfires of 2003, hectares of imported species were killed, but in a matter of weeks the gum trees were putting out suckers and looking generally healthy.

The two valuable timber trees, Alpine Ash E. delegatensis and Mountain Ash E. regnans, are killed by fire and only regenerate from seed. The same fire that has had little impact on forests around Canberra has resulted in thousands of hectares of dead ash forests. There has been some debate as to whether to leave the stands, or attempt to harvest the mostly undamaged timber.

Cultivation and uses

Eucalypts have many uses which have made them economically important trees. Perhaps the Karri and the Yellow box varieties are the best known. Due to their fast growth the foremost benefit of these trees is the wood. They provide many desirable characteristics for use as ornament, timber, firewood and pulpwood. Fast growth also makes eucalypts suitable as windbreaks.

Eucalypts draw a tremendous amount of water from the soil through the process of transpiration. They have been planted (or re-planted) in some places to lower the water table and reduce soil salination. Eucalypts have also been used as a way of reducing malaria by draining the soil in Algeria, Sicily[2] and also in Europe and California[3]. Drainage removes swamps which provide a habitat for mosquito larvae, but such drainage can also destroy ecologically productive areas.

Eucalyptus oil is readily steam distilled from the leaves and can be used for cleaning, deodorising, and in very small quantities in food supplements; especially sweets, cough drops and decongestants.

The nectar of some eucalyptus produces high quality monofloral honey. In the western United States the flowering is in late January, before the flowering of commercial nut and fruit trees, thus it is easily segragated and the honey produced has a flavour described as "buttery .

The ghost gum's leaves were used by Aborigines to catch fish. Soaking the leaves in water releases a mild tranquiliser which stuns fish temporarily.

Eucalyptus is also used to make the digeridoo, a musical wind instrument made popular by the Aborigines of Australia.

Plantation and ecological problems

Eucalyptus were first introduced to the rest of the world by Sir Joseph Banks, botanist on the Cook expedition in 1770. They have subsequently been introduced to many parts of the world, notably California, Brazil, Morocco, Portugal, South Africa, Israel and Galicia. Several species have become invasive and are causing major problems for local ecologies. In Spain, they have been planted in pulpwood plantations, replacing native oak woodland. As in other such areas, while the original woodland supports numerous species of native animal life (insects, birds, salamanders, etc.), the eucalypt groves are inhospitable to the local wildlife which is not adapted to them, leading to silent forests and the decline of wildlife populations.

On the other hand, eucalyptus are the basis for several industries, such as sawmilling, pulp, charcoal and others.

California

In the 1850s many Australians traveled to California to take part in the California Gold Rush. Much of California has similar climate to parts of Australia and some people got the idea of introducing eucalyptus. By the early 1900s thousands of acres of eucalyptus were planted with the encouragement of the state government. It was hoped that they would provide a renewable source of timber for construction and furniture making. However this did not happen partly because the trees were cut when they were too young and partly because the Americans did not know how to process the cut trees to prevent the wood from twisting and splitting.

One way in which the eucalyptus, mainly the blue gum E. globulus, proved valuable in California was in providing windbreaks for highways, orange groves, and other farms in the mostly treeless central part of the state. They are also admired as shade and ornamental trees in many cities and gardens.

Eucalyptus forests in California have been criticized because they drive out the native plants and do not support native animals. Fire is also a problem. The 1991 Oakland Hills firestorm which destroyed almost 3,000 homes and killed 25 people was partly fueled by large numbers of eucalyptus in the area close to the houses

In some parts of California eucalyptus forests are being removed and native trees and plants restored. Individuals have also illegally destroyed some trees and are suspected of introducing insect pests from Australia which attack the trees.

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Flax

Scientific classification

Kingdom: Plantae
Division: Magnoliophyta
Class: Magnoliopsida
Order: Malpighiales
Family: Linaceae

Genus: Linum
Species: *L. usitatissimum*

Binomial name Linum usitatissimum

Flax (also known as *Common Flax* or *Linseed*) is a member of the genus Linum in the family Linaceae. The *New Zealand flax* is unrelated. Flax originated in India and was first domesticated in the Fertile Crescent. [1]

It is an erect annual plant growing to 120 cm tall, with slender stems. The leaves are glaucous green, slender lanceolate, 2-4 cm long and 3 mm broad. The flowers are pure pale blue, 1.5-2.5 cm diameter, with five petals. The fruit is a round, dry capsule 5-9 mm diameter, containing several glossy brown seeds shaped like an apple pip, 4-7 mm long.

In addition to the plant itself, flax may refer to the unspun fibres of the flax plant.

Uses

Flax is grown both for seed and for fibre. Various parts of the plant have been used to make fabric, dye, paper, medicines, fishing nets and soap. It is also grown as an ornamental plant in gardens, as flax is one of the few plant species that is capable of producing truly blue flowers (most "blue" flowers are really shades of purple), although not all flax varieties produce blue flowers.

Flax seed

The seeds produce a vegetable oil known as linseed oil or flaxseed oil. It is one of the oldest commercial oils and solvent-processed flax seed oil has been used for centuries as a drying oil in painting and varnishing. Flax seeds come in two basic varieties; brown and yellow (also referred to as golden). Although brown flax can be consumed and has been for thousands of years, it is better known as an ingredient in paints, fibre and cattle feed. Brown and yellow flax have similar nutritional values and equal amounts of short-chain omega-3 fatty acids. The exception is a type of yellow flax called solin which is very low in omega-3 and has a completely different oil profile. A number of studies have shown that people have a very hard time absorbing the Omega-3 from flaxseed oil compared to oily fish (see Fish and plants as a source of Omega-3 for more).

A North Dakota State University research project led to the creation of a new variety of the yellow flax seed called "Omega"[2]. This new variety was created primarily as a food source and has a more pleasant nutty-buttery flavour than the brown variety and retains a comparable level of the beneficial Omega-3 oil.

One tablespoon of ground flax seeds and three tablespoons of water may serve as a replacement for one egg in baking by binding the other ingredients together, and ground flax seeds can also be mixed in with oatmeal, yogurt, water (similar to Metamucil), or any other food item where a nutty flavour is appropriate. Flaxseed oil is most commonly consumed with salads or in capsules. Flax seed owes its nutritional benefits to lignans and omega-3 essential fatty acids. Omega-3s, often in short supply in populations with low-fish diets, promote heart health by reducing cholesterol, blood pressure and plaque formation in

arteries. In addition, flaxseed oil is often recommended as a galactagogue. Lignans benefit the heart and possess anti-cancer properties: A series of research studies by Lilian U. Thompson and her colleagues at the Department of Nutritional Science of the University of Toronto have reported that flaxseed can have a beneficial effect in reducing tumour growth in mice, particularly the kind of tumour found in human post-menopausal breast cancer. The effects are thought to be due to the lignans in flaxseed, and are additive with those of tamoxifen, the currently standard drug treatment for these cancers. Initial studies suggest that flaxseed taken in the diet have similar beneficial effects in human cancer patients. Reports that flaxseed is beneficial in other cancers, e.g. prostate cancer, are less numerous but promising.

Flax seed sprouts are edible, with a slightly spicy flavour.

Flax fibre

Flax fibres are amongst the oldest fibre crops in the world. The use of flax for the production of linen goes back 5000 years. Pictures on tombs and temple walls at Thebes depict flowering flax plants. The use of flax fibre in the manufacturing of cloth in northern Europe dates back to pre-Roman times. In North America, flax was introduced by the Pilgrim fathers. Currently most flax produced in the USA and Canada are seed flax types for the production of linseed oil or flaxseeds for human nutrition.

Flax fibre is extracted from the bast or skin of the stem of flax plant. Flax fibre is soft, lustrous and flexible. It is stronger than cotton fibre but less elastic. The best grades are used for linen fabrics such as damasks, lace and sheeting. Coarser grades are used for the manufacturing of twine and rope. Flax fibre is also a raw material for the high-quality paper industry for the use of printed banknotes and rolling paper for cigarettes.

Cultivation

The major fibre flax-producing countries are the former USSR, Poland, France, Belgium, Ireland, and the Czech Republic.

The soils most suitable for flax, besides the alluvial kind, are deep friable loams, and containing a large proportion of organic matter. Heavy clays are unsuitable, as are soils of a gravelly or dry sandy nature.

Flax is harvested for fibre production when still green, before seed maturation as the fibre starts to degrade later; it is pulled up with the roots (not cut), so as to maximise the fibre length. Immediately after harvesting, it is put in water to soak (retting) to rot off the non-fibrous material in the stems. Retting takes 7-12 days, depending on temperature.

Flax grown for seed is allowed to mature until the seed capsules are yellow and just starting to split; it is then harvested by combine harvester and dried to extract the seed.

Threshing flax

The process is divided into two parts: the first part is intended for the farmer, or flax-grower, to bring the flax into a fit state for general or common purposes. This is performed

by three machines: one for threshing out the seed, one for breaking and separating the wood from the fibre, and one for further separating the broken wood and matter from the fibre. In some cases the farmers will perhaps thrash out the seed in their own mill and therefore, in such cases, the first machine will be, of course, unnecessary.

The second part of the process is intended for the manufacturer to bring the flax into a state for the very finest purposes, such as lace, cambric, damask, and very fine linen. This second part is performed by the refining machine only.

The threshing process would be conducted as follows:

- Take the flax in small bundles, as it comes from the field or stack, and holding it in the left hand, put the seed end between the threshing machine and the bed or block against which the machine is to strike; then take the handle of the machine in the right hand, and move the machine backward and forward, to strike on the flax, until the seed is all threshed out.
- Take the flax in small handfuls in the left hand, spread it flat between the third and little finger, with the seed end downwards, and the root-end above, as near the hand as possible.
- Put the handful between the beater of the breaking machine, and beat it gently till the three or four inches, which have been under the operation of the machine, appear to be soft.
- Remove the flax a little higher in the hand, so as to let the soft part of the flax rest upon the little finger, and continue to beat it till all is soft, and the wood is separated from the fibre, keeping the left hand close to the block and the flax as flat upon the block as possible.
- The other end of the flax is then to be turned, and the end which has been beaten is to be wrapped round the little finger, the root end flat, and beaten in the machine till the wood is separated, exactly in the same way as the other end was beaten.

Trivia

- Common flax is the national flower of Belarus.
- Flax is the emblem of the Northern Ireland Assembly.
- The flax plant appeared on the reverse of the UK one pound coin to represent Northern Ireland on coins minted in 1986 and 1991.
- In English, blond hair is traditionally referred to as "fair" or "flaxen".

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See also

- Linseed oil

Ginger

Zingiber officinale
Conservation status: Secure

Scientific classification

Kingdom: Plantae
Division: Magnoliophyta
Class: Liliopsida
Order: Zingiberales
Family: Zingiberaceae
Genus: Zingiber
Species: *Z. officinale*

Binomial name: Zingiber officinale, Roscoe

Though called a root, it is actually the rhizome of the monocotyledonous perennial plant Zingiber officinale.

Originating in southern China, cultivation of ginger spread to India, Southeast Asia, West Africa, and the Caribbean.[1]

The English word ginger is etymologically related to the Tamil iñci (‡žÍš¿), having been borrowed into Indo-European languages from a Dravidian language. [2]

Chemistry

Ginger contains up to 3% of an essential oil that causes the fragrance of the spice. The main constituents are sesquiterpenoids with (-)-zingiberene as the main component. Lesser amounts of other sesquiterpenoids (^{2}-sesquiphellandrene, bisabolene and farnesene) and a small monoterpenoid fraction (^{2}-phelladrene, cineol, and citral) have also been identified.

The pungent taste of ginger is due to nonvolatile phenylpropanoids (particularly gingerol and zingerone) and diarylheptanoids (gingeroles and shoagoles); the latter are more

pungent and form from the former when ginger is dried. Cooking ginger transforms gingerol into zingerone, which is less pungent and has a spicy-sweet aroma.[3] None of these pungent chemicals are related to capsaicin, the principal hot constituent of chile pepper.

Culinary uses

Young ginger roots are juicy and fleshy with a very mild taste. They are often pickled in vinegar or sherry as a snack or just cooked as an ingredient in many dishes. They can also be stewed in boiling water to make ginger tea, to which honey is often added as a sweetener. Mature ginger roots are fibrous and nearly dry. The juice from old ginger roots is extremely potent and is often used as a spice in Chinese cuisine to flavor dishes that incorporate certain meats like seafood and mutton.

Ginger is also candied, is used as a flavoring for candy, cookies, crackers and cake, and is the main flavor in ginger ale, a sweet, carbonated, non-alcoholic beverage, as well as the similar, but somewhat spicier beverage ginger beer. A ginger-flavored liqueur called Canton is produced in the Guangdong province of China; it is advertised to be based on a recipe created for the rulers of the Qing Dynasty and made from six different varieties of ginger. Green ginger wine is a ginger flavoured wine produced in the United Kingdom by Crabbie's and Stone's and traditionally sold in a green glass bottle. Ginger is also used as a spice added to hot coffee and tea.

In Japan, ginger is pickled to make beni shoga and gari or grated and used raw on tofu or noodles.

In Western cuisine, ginger is traditionally restricted to sweet foods, such as ginger ale, gingerbread, ginger snaps, ginger cake and ginger biscuits.

Powdered dry ginger (ground ginger) is typically used to add spiciness to gingerbread and other recipes. Ground and fresh ginger taste quite different and ground ginger is a particularly poor substitute for fresh ginger. Fresh ginger can be successfully substituted for ground ginger and should be done at a ratio of 6 parts fresh for 1 part ground. You generally achieve better results by substituting only half the ground ginger for fresh ginger.

In Myanmar, ginger is used in a salad dish called gyin-tho, which consists of shredded ginger preserved in oil, and a variety of nuts and seeds.

In traditional Korean Kimchi, ginger is minced finely and added into the ingredients of the spicy paste just before the fermenting process.

In India, ginger is used in all sub-varieties of the indian cuisines. In south India, ginger is used in the production of a candy called Inji-murappa ("ginger candy" from Tamil). This candy is mostly sold by vendors to bus passengers in bus stops and in small tea shops as a locally produced item. Candied ginger is also very famous around these parts. Additionally, in Tamil Nadu, especially in the Tanjore belt, a variety of ginger which is less spicy is used when tender to make fresh pickle with the combination of lemon juice, salt and tender green chillies. This kind of pickle was generally made before the invention of refrigeration and stored for a maximum of 4-5 days. The pickle gains a mature flavor when the juices cook the ginger over the first 24 hours.

In South East Asia, the flower of a type of ginger is used in cooking. This unopened flower is known in the Malay language as Bunga Kantan, and is used in salads and also as garnish for sour-savoury soups, like Assam Laksa.

Ginger has a sialagogue action, stimulating the production of saliva.

Medicinal uses

Medical research has shown that ginger root is an effective treatment for nausea caused by motion sickness or other illness,[4][5] and also contains many antioxidants. Powdered dried ginger root is made into capsules for medicinal use. Modern research on nausea and motion sickness used approximately 1 gram of ginger powder daily. Although very effective against all forms of nausea, PDR health officials do not recommend taking ginger root for morning sickness commonly associated with pregnancy, though Chinese women traditionally eat ginger root during pregnancy to combat morning sickness. The Natural Medicines Comprehensive Database (compiled by health professionals and pharmacists), states that ginger is likely safe for use in pregnancy when used orally in amounts found in foods. Ginger ale and ginger beer have been recommended as "stomach settlers" for generations in countries where the beverages are made. Ginger water was commonly used to avoid heat cramps in the United States in the past. Research has also found ginger to be a powerful antioxidant. Ginger has also been shown in research to have a regulatory role in the natural inflammatory response of the body. In India ginger is applied as a paste to the temples to relieve headache.

Ginger has also been commonly used to treat inflammation, although medical studies as to the efficacy of ginger in decreasing inflammation have shown mixed results. There are several studies that demonstrate very positive results on minimizing joint pain from arthritis and other inflammatory disorders. It may also have blood thinning and cholesterol lowering properties, making it effective in treating heart disease; while early studies have shown some efficacy, it is too early to determine whether further research will bear this out.[1]

The characteristic odor and flavor of ginger root is caused by a mixture of zingerone, shoagoles and gingerols, volatile oils that compose about 1%–3% by weight of fresh ginger. The gingerols have analgesic, sedative, antipyretic, antibacterial, and GI tract motility effects.

Ginger is on the GRAS list from FDA. However, like other herbs, ginger may be harmful because it may interact with other medications, such as warfarin; hence, a physician or pharmacist should be consulted before taking the herb as a medicinal agent or on a long-term basis. Ginger is also contraindicated in people suffering from gallstones, because the herb promotes the release of bile from the gallbladder [2]. Ginger can also be used to prevent scurvy.

Ginger allergies

Some people are allergic to ginger. Generally, this is reported as having a gaseous component. This may take the form of flatulence, or it may take the form of an extreme constriction or tightening in the throat necessitating uncontrollable burping to relieve the pressure.

Gardening

Ginger produces clusters of white and pink flower buds that bloom into yellow flowers. Because of the aesthetic appeal and the adaptivity of the plant to warm climates, ginger is often used as landscaping around subtropical homes.

Reference in Popular Culture

To members of the Race, an alien species in Harry Turtledove's best-selling novel series, Worldwar, ginger is a highly addictive, psychoactive drug, with an effect similar to that of cocaine or PCP in humans.

In Cockney rhyming slang, ginger is a derogatory euphemism for homosexual. The original slang rhymed queer with ginger beer.

In the west of Scotland (particularly Glasgow), ginger is a term for any soft drink.

Similar species

Myoga (Zingiber mioga Roscoe) appears in Japanese cuisine; the flower buds are the part eaten.

Another plant in the Zingiberaceae family, galangal, is used for similar purposes as ginger in Thai cuisine. Galangal is also called Thai ginger. Also referred to as galangal, fingerroot (Boesenbergia rotunda), or Chinese ginger or the Thai krachai, is used in cooking and medicine.

A dicotyledonous native species of eastern North America, Asarum canadense, is also known as "wild ginger", and its root has similar aromatic properties, but it is not related to true ginger and should not be used as a substitute because it contains the carcinogen aristolochic acid. This plant is also a powerful diuretic, or urinary stimulator. It is part of the Aristolochiaceae family.

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Ginkgo

Conservation status: Endangered

Scientific classification

Kingdom: Plantae
Division: *Ginkgophyta*
Class: *Ginkgoopsida*
Order: *Ginkgoales*
Family: *Ginkgoaceae*
Genus: *Ginkgo*
Species: *G. biloba*

Binomial name: *Ginkgo biloba*

The *Ginkgo* (*Ginkgo biloba*), frequently misspelled as "Gingko", and sometimes known as the *Maidenhair Tree*, is a unique tree with no close living relatives. It is classified in its own division, the *Ginkgophyta*, comprising the single class *Ginkgoopsida*, order *Ginkgoales*, family *Ginkgoaceae*, genus *Ginkgo* and just the one species. It is one of the best known examples of a living fossil. In the past it has also been placed in the divisions Spermatophyta or Pinophyta. Ginkgo is a gymnosperm (as opposed to an angiosperm), meaning "naked seed"; its seeds are not protected by an ovary wall and hence, the berry-like structures produced by female ginkgo trees are technically not fruit.

For centuries it was thought to be extinct in the wild, but is now known to grow wild in at least two small areas in Zhejiang province in eastern China, in the Tian Mu Shan Reserve. However, as this area has known human activity for over a thousand years, the wild status of ginkgos there is uncertain.

Characteristics

Habit

Ginkgos are medium-large deciduous trees, reaching 20–35 m tall (some specimens in China being over 50 m), with an often angular crown and long, somewhat erratic branches. They are usually deep rooted and resistant to wind and snow damage. Young trees are often tall and slender, and sparsely branched; the crown becomes broader as the tree ages. During autumn, the leaves turn a bright yellow, then fall, sometimes within a short space of time (1–15 days). A combination of amazing disease resistance, insect-resistant wood and the ability to form aerial roots and sprouts means that ginkgos are very long-lived, with some specimens claimed to be more than 2,500 years old; a 3,000 year-old ginkgo is reported in Shandong province in China (Lewington and Parker, 183).

Some old Ginkgos produce aerial roots, known as chichi (Japanese; "nipples") or zhong-ru (Chinese), which form on the undersides of large branches and grow downwards. Chichi

growth is very slow, and may take hundreds of years to occur. The function, if any, of these thick aerial roots is unknown.

Stem

Ginkgo branches grow in length by growth of shoots with regularly spaced leaves, as seen on most trees. From the axils of these leaves, "spur shoots" (also known as short shoots) develop on second-year growth. Short shoots have very short internodes (so that several years' growth may only extend them by a centimeter or two) and their leaves are ordinarily unlobed. They are short and knobby, and are arranged regularly on the branches except on first-year growth. Because of the short internodes, leaves appear to be clustered at the tips of short shoots, and reproductive structures are formed only on them (see picture to above left—seeds and leaves can be viewed on short shoots). In Ginkgos, as in other plants that possess them, short shoots allow the formation of new leaves in the older parts of the crown. After a number of years, a short shoot may change into a long (ordinary) shoot, or vice versa.

Leaves

The leaves are unique among seed plants, being fan-shaped with veins radiating out into the leaf blade, sometimes bifurcating (splitting) but never anastomosing to form a network. Two veins enter the leaf blade at the base and fork repeatedly in two; this is known as dichotomous venation. The leaves are 5-10 cm (rarely to 15 cm) long. The old popular name "Maidenhair tree" is because the leaves resemble some of the pinnae of the Maidenhair fern Adiantum capillus-veneris.

Leaves of long shoots are usually notched or lobed, but only from the outer surface, between the veins. They are borne both on the more rapidly-growing branch tips, where they are alternate and spaced out, and also on the short, stubby spur shoots, where they are clustered at the tips. During summer the leaves are a deep green, turning to brilliant yellow in the fall. They generally remain yellow for a time, then suddenly drop most of their leaves in what can seem like overnight.

Reproduction

Ginkgos are dioecious, with separate sexes, some trees being female and others being male. Male plants produce small pollen cones with sporophylls each bearing two microsporangia spirally arranged around a central axis.

Female plants do not produce cones. Two ovules are formed at the end of a stalk, and after pollination, one or both develop into seeds. The seed is 1.5-2 cm long. Its outer layer (the sarcotesta) is light yellow-brown, soft, and fruit-like. It is plum-like and attractive, but the seed coat contains butanoic acid and smells like rancid butter (which contains the same chemical) when fallen on the ground. Beneath the sarcotesta is the hard sclerotesta and a papery endotesta and nucellus.

The fertilization of ginkgo seeds is by motile sperm; similar to cycads, ferns, mosses and the algae. It is a large sperm of about 250-300 micrometres, similar to the cycad which is a

little larger. It was first discovered by the Japanese botanist Sakugoro Hirase in the early 1900s. The sperm has a complex multi-layered structure which is a continuous belt of basal bodies that form the base of several thousand flagella which actually have a cilia-like motion. The flagella/cilia apparatus pulls the body of the sperm forwards. But it has only a tiny distance to travel to the archegonia, of which there are usually two or three. Two sperm are produced, one of which successfully fertilizes the ovule. Although it is widely held that fertilization of ginkgo seeds occurs just before or after they fall in early autumn, [2] [3][4] embryos ordinarily occur in seeds just before and after they drop from the tree. [5]

Name

The name ginkgo means "silver apricot" (€O, pinyin: yínxìng) in Chinese. The same characters are used in Japanese and Korean (where the ginkgo had been introduced from China). The Japanese pronunciation is ichM while the Korean equivalent is eunhang, both of which appear to be a loan from Chinese, though this is not certain (from the entry in the dictionary KMjien). The Japanese characters used to write ginkgo look as though they could be read ginkyM, and this was the name Engelbert Kaempfer, the first Westerner to see the species in 1690, wrote down in his Amoenitates Exoticae (1712). However, his y was misread as a g, and the misspelling stuck.

In modern Japanese, the characters are read either ichM (meaning the tree) or ginnan (meaning the seed); this latter reading appears to be based on the renjM (i.e., liaison) reading of the characters. The modern Chinese name for its shelled seeds is }œ (Mandarin bái guÒ), meaning "white fruit".

Prehistory

The Ginkgo is a living fossil, with fossils recognisably related to modern Ginkgo from the Permian, dating back 270 million years. They diversified and spread throughout Laurasia during the middle Jurassic and Cretaceous, but became much rarer thereafter. By the Paleocene, Ginkgo adiantoides was the only Ginkgo species left in the Northern Hemisphere (but see below) with a markedly different (but not well-documented) form persisting in the Southern Hemisphere, and at the end of the Pliocene Ginkgo fossils disappeared from the fossil record everywhere apart from a small area of central China where the modern species survived. It is in fact doubtful whether the Northern Hemisphere fossil species of Ginkgo can be reliably distinguished; given the slow pace of evolution in the genus, there may have been only 2 in total; what is today called G. biloba (including G. adiantoides), and G. gardneri from the Paleocene of Scotland.

At least morphologically, G. gardneri and the Southern Hemisphere species are the only known post-Jurassic taxa that can be unequivocally recognised, the remainder may just as well have simply been ecotypes or subspecies. The implications would be that G. biloba had occurred over an extremely wide range, had remarkable genetic flexibility and though evolving genetically never showed much speciation. The occurrence of G. gardneri, it seems a Caledonian mountain endemic, and the somewhat greater diversity on the Southern Hemisphere, suggests that old mountain ranges on the Northern Hemisphere could hold other, presently undiscovered, fossil Ginkgo species. Since the distribution of Ginkgo was

already relictual in late prehistoric times, the chances that ancient DNA from subfossils can shed any light on this problem seem remote. While it may seem improbable that a species may exist as a contiguous entity for many millions of years, many of the Ginkgo's life-history parameters fit. These are extreme longevity, slow reproduction rate, (in Cenozoic and later times) a wide, apparently contiguous, but steadily contracting distribution coupled with, as far as can be demonstrated from the fossil record, extreme ecological conservatism (being restricted to light soils around rivers), and a low population density.

Ginkgophyta fossils have been classified in the following families and genera:

- Ginkgoaceae
  - Arctobaiera
  - Baiera
  - Eretmophyllum
  - Ginkgo
  - Ginkgoites
  - Sphenobaiera
  - Windwardia
- Trichopityaceae
  - Trichopitys

Ginkgo has been used for classifying plants with leaves that have more than four veins per segment, while Baiera for those with less than four veins per segment. Sphenobaiera has been used to classify plants with a broadly wedge-shaped leaf that lacks a distinct leaf stem. Trichopitys is distinguished by having multiple-forked leaves with cylindrical (not flattened) thread-like ultimate divisions; it is one of the earliest fossils ascribed to the Ginkgophyta.

Ginkgo has long been cultivated in China; some planted trees at temples are believed to be over 1,500 years old. The first record of Europeans encountering it is in 1690 in Japanese temple gardens, where the tree was seen by the German botanist Engelbert Kaempfer. Because of its status in Buddhism and Confucianism, the Ginkgo is also widely planted in Korea and parts of Japan; in both areas, some naturalization has occurred, with Ginkgos seeding into natural forests.

In some areas, notably the United States, most intentionally-planted Ginkgos are male cultivars grafted onto plants propagated from seed, because the male trees will not produce the malodorous seeds. The popular cultivar 'Autumn Gold' is a clone of a male plant.

The Ginkgo has the intriguing distinction of being one of the world's most urban-tolerant trees, often growing where other trees cannot survive. Some claim that only one tree species, the Tree-of-heaven, is as urban-tolerant. Ginkgos rarely suffer disease problems, even in urban conditions, and are attacked by few insects. For this reason, and for their general beauty, ginkgos are excellent urban and shade trees, and are widely planted along many streets. The ginkgo is the official tree of the city of Kumamoto, and two leaves form the symbol of the University of Tokyo, the main campus of which is famous for its numerous ginkgos.

Ginkgos are also popular subjects for growing as penjing and bonsai; they can be kept artificially small and tended over centuries. Furthermore, the trees are easy to propagate from seed.

Extreme examples of the Ginkgo's tenacity may be seen in Hiroshima, Japan, where four trees growing between 1–2 km from the 1945 atom bomb explosion were among the few living things in the area to survive the blast (photos & details). While almost all other plants (and animals) in the area were destroyed, the ginkgos, though charred, survived and were healthy. The trees are alive to this day.

Culinary use

The nut-like gametophytes inside the seeds are esteemed in and outside of Asia, and are a traditional Chinese food (e.g. congee, often served at weddings), and are believed to have health benefits; some also consider them to have aphrodisiac qualities. Japanese cooks add Ginkgo seeds to dishes such as chawanmushi, and cooked seeds are often eaten along with other dishes. The seeds are available canned, sold as "White Nuts", and can be found in many Asian food stores in the West. Usually only a few are added for a portion enough for ten people.

When eaten by children, in large quantities (over 5 seeds a day), or over a long period of time, the raw gametophyte (meat) of the seed can cause poisoning by MPN (4-methoxypyridoxine). MPN is heat-stable. Studies have demonstrated that convulsions caused by MPN can be prevented or terminated with pyridoxine.

Some people are sensitive to the chemicals in the sarcotesta, the outer fleshy coating. These people should handle the seeds with care when preparing the seeds for consumption, wearing disposable gloves. The symptoms are dermatitis or blisters similar to that caused by contact with poison-ivy. However, seeds with the fleshy coating removed are perfectly safe to handle.

Medical uses

The extract of the Ginkgo leaves contains flavonoid glycosides and ginkgolides and has been used pharmaceutically. It has many alleged nootropic properties, and is mainly used as memory enhancer and anti-vertigo agent. However, studies differ about its efficacy.

Out of the many conflicting research results, there seem to be basically three effects of Ginkgo extract on the human body: it improves blood flow (including microcirculation in small capillaries) to most tissues and organs; it protects against oxidative cell damage from free radicals (antioxidant); and it blocks many of the effects of PAF (platelet aggregation, blood clotting) that have been related to the development of a number of cardiovascular, renal, respiratory and CNS (Central Nervous System) disorders. Ginkgo can be used for intermittent claudication.

A 2004 conference paper [6] summarises how various trials indicate that Ginkgo shows promise in the treatment of Alzheimer's disease, although further study is needed.

Ginkgo is commonly added to energy drinks, but the amount is typically so low it does not produce a noticeable effect, except perhaps via a placebo effect from Ginkgo being listed on the label.

Side effects

Ginkgo may have some undesirable effects, especially for individuals with blood circulation disorders and those taking anti-coagulants such as aspirin and warfarin, although recent studies have found that ginkgo has little or no effect on the anticoagulant properties or pharmacodynamics of warfarin[7][8]. Ginkgo should also not be used by people who are taking monoamine oxidase inhibitors (MAOI) or by pregnant women without first consulting a doctor.

Ginkgo side effects and cautions include: possible increased risk of bleeding, gastrointestinal discomfort, nausea, vomiting, diarrhea, headaches, dizziness, and restlessness.

If any side effects are experienced consumption should be halted immediately. Ginkgo supplements are usually taken in the range of 40–200 mg per day. If the side effects continue usage should be stopped completely.

See also

- Herbalism

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Hop

Scientific classification

Kingdom: Plantae
Division: Magnoliophyta
Class: Magnoliopsida
Order: Rosales
Family: Cannabaceae
Genus: *Humulus*

Species

Humulus lupulus L.
Humulus japonicus Siebold & Zucc.
Humulus yunnanensis Hu

The *hop* (Humulus) is a small genus of flowering plants, native to the temperate Northern Hemisphere. The female flowers, commonly called hops, are used as flavouring and stabilisers during beer brewing.

Although frequently referred to as the *hop vine*, it is technically a bine; unlike vines, which use tendrils, suckers, and other appendages for attaching themselves, bines have stout stems with stiff hairs to aid in climbing. It is a perennial herbaceous plant which sends up new shoots in early spring and dies back to the cold-hardy rhizome in autumn. Hop shoots grow very rapidly and at the peak of growth can grow 20–50 cm per week. Hop bines climb by wrapping clockwise around anything within reach, and individual bines typically grow between 2 to 15 m depending on what is available to grow on. The leaves are opposite, with a 7–12 cm petiole and a cordate-based, palmately lobed blade 12–25 cm long and broad; the edges are coarsely toothed. When the hop bines run out of material to climb, horizontal shoots sprout between the leaves of the main stem to form a network of stems wound round each other.

Species

There are three species, one with five varieties:

- Humulus japonicus (syn. H. scandens). *Asian Hop*. Leaves with 5–7 lobes. Eastern Asia.
- Humulus lupulus. *Common Hop*. Leaves with 3–5 lobes. Europe, western Asia, North America.
    - Humulus lupulus var. lupulus. Europe, western Asia.
    - Humulus lupulus var. cordifolius. Eastern Asia.
    - Humulus lupulus var. lupuloides (syn. H. americanus). Eastern North America.
    - Humulus lupulus var. neomexicanus. Western North America.

  - Humulus lupulus var. pubescens. Midwest North America.
- Humulus yunnanensis. *Yunnan Hop*. Leaves with 3–5 lobes, densely hairy below. Southeast Asia (endemic in Yunnan, China).

Brewers' hops are specific cultivars, propagated by asexual reproduction.

Cultivation

History

The first documented instance of hop cultivation was in 736, in the Hallertau region of present-day Germany (which is today the most important production centre with about 25% of the worldwide production), although the first mention of the use of hops in brewing was in 1079. Hops were introduced to British beers in the early 1500s, and hop cultivation began in the present-day United States in 1629.

Today, the principal production centres for the UK are in Kent (which produces Kent Golding hops) and Worcestershire, and Washington state for the USA; other important production areas include Belgium, as mentioned Germany and the Czech Republic. Other major areas of production include Xinjiang (China), Tasmania (Australia), the Lublin area (Poland) and Chuvashia (Russia). New Zealand is a leading centre for organic hop production.

Until mechanisation (in the late 1960s for the UK), the need for massed labour at harvest time meant hop-growing had a big social impact. Many of those hopping in Kent were Eastenders, for whom the annual migration meant not just money in the family pocket but a welcome break from the grime and smoke of London. Whole families would come down on special trains and live in hoppers' huts for most of September, even the smallest children helping in the fields. In Kent, hops areas had Oast houses built for drying the hops; many now are converted to homes. The image of Cockney hoppers beneath the blue September skies of the Battle of Britain in 1940 has become part of British national mythology. Romany travellers were another very large group among the hoppers.

Propagation and pests

The European Hop is propagated either by nursery plants or by cuttings. These are set in "hills", formed by digging holes in the spring, which are filled with fine leaf mould. The density of the holes varies from 3–5 holes per m^2. One, two, or three plants are put in each hill; although, if hops are designed to be raised from cuttings, four or five of these, ranging from 7 to 10 cm (3–4 inches) in length, are planted 3–5 cm deep in fine leaf mould.

Hop growing, though profitable when it succeeds, is risky, with several significant insect pests causing damage, including the European Corn Borer Ostrinia nubilalis and the Hop froghopper Aphrophora interrupta. Hop gardens on chalky soils are particularly subject to damage. In June and July, the hops are liable to be damaged by an aphid, Myzus humuli. This insect, however, does not endanger the growth of the plant, unless it is already in a weak state from root damage by the larvae of the ottermoth, Phalaena humuli. The roots are also attacked by the larvae of Common Swift, Ghost Moth and Orange Swift. The foliage is

sometimes eaten by the larvae of other Lepidoptera including Angle Shades, Currant Pug, Emperor Moth, The Gothic and Hebrew Character.

Harvest

At the end of the first year it becomes necessary to put poles into the hills, around which the bines reared from plants are wound; at the expiration of the second year, full-sized poles, from 5–6 m long, are set (though the hop bines will run to the height of 15 m) in the proportion of two poles to each hill, and a similar number of hop-plants are fastened loosely round each pole, by means of withered rushes.

In the northern hemisphere, hops begin to flower about the latter end of June or the beginning of July, at which point the poles are now entirely covered with foliage, and the pendent flowers are appearing in clusters. The hops themselves, which are the scaly seed-vessels of the female plants, are picked off by hand when the seed is formed around the end of August; for this purpose the poles are often taken down with the plants clinging to them. The seed-vessels are then dried, exposed to the air for a few days, and packed in sacks and sent to market.

Production

The 2005 world production of hops according to FAOSTAT was as follows;

- Germany 29,000 tonnes
- USA 26,180 tonnes
- China 20,000 tonnes
- Czech Republic 6,800 tonnes
- Poland 3,355 tonnes
- Australia 2,000 tonnes
- North Korea 2,000 tonnes
- UK 2,000 tonnes
- Slovenia 1,500 tonnes
- France 1,400 tonnes

The total world production for 2005 was 102,216 tonnes.

Uses

Beer

Hop resins are composed of two main acids: alpha and beta acids. Alpha acids have a mild antibiotic/bacteriostatic effect against Gram-positive bacteria, and favours the exclusive activity of brewing yeast in the fermentation of beer. The flavour imparted by hops varies greatly by variety and use: hops boiled with the beer (known as "bittering hops") produce bitterness, while hops added to beer later impart some degree of "hop flavour" (if during the final 10 minutes of boil) or "hop aroma" (if during the final 3 minutes, or less, of boil) and a lesser degree of bitterness. Adding hops after the boil, a process known as "dry hopping",

adds hop aroma, but very little bitterness. The degree of bitterness imparted by hops depends on the degree to which otherwise insoluble alpha acids (AAs) are isomerised during the boil, and the impact of a given amount of hops is specified in International Bitterness Units. Unboiled hops are only mildly bitter. Beta acids do not isomerise during the boil of wort, and have a negligible effect on beer flavour. Instead they contribute to beer's bitter aroma, and high beta acid hop varieties are often added at the end of the wort boil for aroma. Beta acids oxidise and oxidised beta acids form sulphur compounds such as DMS (dimethyl-sulfide) that can give beer off-flavours of rotten vegetables or cooked corn.

"Noble hops" are low in bitterness and high in aroma, and traditionally consist of four central European cultivars, 'Hallertauer Mittelfrueh', 'Tettnanger', 'Spalter', and 'Saaz'. They contain high amounts of the hop oil humulene and low amounts of alpha acids cohumulone and adhumulone, as well as lower amounts of the harsher-tasting beta acids lupulone, colupulone, and adlupulone. Humulene imparts an elegant, refined taste and aroma to beers containing it. These hops are used in pale lagers.

English ales use hop varieties such as Fuggle, Golding and Bullion. North American varieties include Cascade, Columbia, and Willamette. Certain beers (particularly the highly-hopped style known as India Pale Ale) can have high levels of bitterness.

Flavours and aromas are described using terms which include "grassy", "floral", "citrus", "spicy", and "earthy".

Medicinal use

The medically active ingredients in Hops are humulene and lupulene.

Dried female buds have a high methylbutenol content, which has a mild sedative effect on the central nervous system; it is used in the treatment for insomnia, stress and anxiety. If one has trouble getting sleep, hop tea before going to bed may help, though a quantity of beer has similar results.

Hops' antibacterial qualities also stimulate gastric juice production.

Fibre

The stem is flexible and very tough, with a tenacious fibre that has been used in some cases to make cloth and paper.

Other uses

Tender young hop shoots, which are only available for about three weeks during spring, were mainly eaten by the poor in medieval times, and was a substitute for asparagus. Only recently have they been rediscovered as a delicacy in parts of Germany, Belgium and England. They are served raw with vinaigrette, or boiled with fresh herbs or fried in batter.

Wild hops are also relished by cows, horses, goats, sheep, and pigs.

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Mistletoe

Scientific classification

Kingdom: Plantae
Division: Magnoliophyta
Class: Magnoliopsida
Order: Santalales

Families

Santalaceae (Viscaceae)
Loranthaceae
Misodendraceae

Mistletoe is the common name for various parasitic plants in the order Santalales, belonging to the families Santalaceae, Loranthaceae and Misodendraceae. The species in Santalaceae were formerly commonly treated in a separate family Viscaceae.

The name was originally applied to Viscum album (European Mistletoe, Santalaceae; the only species native in Great Britain and much of Europe), and subsequently to other related species, including Phoradendron leucarpum (the Eastern Mistletoe of eastern North America, also Santalaceae). In an example of convergent evolution, several less related but superficially very similar plants in the Loranthaceae are also so similar that they have also been called mistletoes.

The European Mistletoe is readily recognised by its smooth-edged oval leaves in pairs along the woody stem, and waxy white berries in dense clusters of 2-6 together. American Mistletoe is similar, but has shorter, broader leaves and longer clusters of ten or more berries together.

Mistletoe biodiversity is markedly higher in subtropical and tropical climates; Australia has 85 species, of which 71 are in Loranthaceae, and 14 in Santalaceae.

The species grow on a wide range of trees, and can eventually prove fatal to them where infestation is heavy, though damage more commonly only results in growth reduction. Most mistletoes are only partial parasites, bearing evergreen leaves that carry out some photosynthesis of their own, relying on the host mainly for mineral nutrients from the ground. The genus Arceuthobium (dwarf mistletoe; Santalaceae) has dispensed with even this, becoming a total parasite relying on its host plant for photosynthesis as well as nutrients.

Most mistletoes are spread by birds (e.g. the Mistle Thrush in Europe, and the Phainopepla in southwestern North America) which eat the berries. The seeds are excreted in their droppings and stick to twigs, or more commonly the bird grips the fruit in its bill, squeezing the sticky coated seed out to the side, and then wiping its bill clean on a suitable branch. The seeds are coated with a sticky gum, viscin, which hardens and attaches the seed firmly to its future host.

The word 'mistletoe' is of uncertain etymology; it may be related to German Mist, another word for dung, but Old English mistel was also used for basil.

While historically often considered a pest that kills trees and devalues natural habitats, mistletoe has recently become recognized as an ecological keystone, an organism that has a disproportionately pervasive influence over its community. A broad array of animals depend on mistletoe for food, consuming the leaves and young shoots as well as transferring pollen between plants and dispersing the sticky fruits. The dense evergreen clumps also make excellent locations for roosting and nesting, with species ranging from Northern Spotted Owls, Marbled Murrelets, Diamond Firetails and Painted Honeyeaters recorded nesting in different mistletoes. This behaviour is probably far more widespread than currently recognised; more than 240 species of birds that nest in foliage in Australia have been recorded nesting in mistletoe, representing more than 75% of the resident avifauna. These interactions lead to dramatic influences on diversity, as areas with greater mistletoe densities support higher diversities of animals. Thus, rather than being a pest, mistletoe can have a positive effect on biodiversity, providing high quality food and habitat for a broad range of animals in forests and woodlands worldwide.

Uses and mythology

The leaves and young twigs are the parts used by herbalists, and it is popular in Europe, especially in Germany, for treating circulatory and respiratory system problems as well as for tumors, even malignant ones.

Mistletoe figured prominently in Norse mythology (whence the modern Western custom of kissing under bunches of it hung as holiday decorations). The god Baldur was killed with a weapon made of mistletoe. In Celtic mythology and in Druid rituals, it was considered an antidote to poison, but contact with its berries produces a rash similar to the poison ivy rash in people who are sensitive to it (as many are), so the whole plant came to be thought of as poisonous.

In Romanian traditions, mistletoe (vâsc in romanian) is considered as a source of good fortune. The medical and the supposed magical properties of the plant are still used, especially in rural areas. This custom is inherited from Dacians.

Mistletoe has sometimes been nick-named the "vampire plant" because it can probe beneath the tree bark to drain water and minerals, enabling it to survive during a drought (see vampirism). William Shakespeare gives it an unflattering reference in Titus Andronicus, Act II, Scene I:

Nowadays, mistletoe is commonly used as a Christmas decoration. Viscum album is used in Europe whereas Phoradendron leucarpum is used in North America. According to a custom of Christmas cheer, any two people who meet under a hanging of mistletoe are obliged to kiss. The origin of this custom may be related to the story of Baldur coming back

to life because of his mother Frigga (or Frigg), the goddess of love who removed the mistletoe's poison with her tears. When Baldur came back to life she kissed everyone who passed underneath the mistletoe out of happiness and gratitude and thus started the custom. Roman sources also mention misletoe was used by the celts in some sort of fertility rite or charm making the practise of kissing under it even more intriguing. Hence why mistletoe is used at Christmas, a time of love and joy.

Mistletoe was the official flower for the State of Oklahoma until 2004 when it was replaced by the Oklahoma Rose. Mistletoe however still serves as the state's official floral emblem.

Oat

Scientific classification

Kingdom: Plantae
Division: Magnoliophyta
Class: Liliopsida
Order: Poales
Family: Poaceae
Genus: Avena
Species: *A. sativa*

Binomial name *Avena sativa*

The *Oat* (Avena sativa) is a species of cereal grain, and the seeds of this plant. They are used for food for people and as fodder for animals, especially poultry and horses. Oat straw is used as animal bedding and sometimes as animal feed.

Since oats are unsuitable for making bread, they are often served as a porridge made from crushed or rolled oats, oatmeal, and are also baked into cookies (oatcakes) which can have added wheat flour. As oat flour or oatmeal, they are also used in a variety of other baked goods and cold cereals, and as an ingredient in muesli and granola. Oats may also be consumed raw, and cookies with raw oats are becoming popular. Oats are also occasionally used in Britain for brewing beer. Oatmeal stout is one variety brewed using a percentage of oats for the wort.

Oats also have non-food uses. Oat straw is also used in corn dolly making, and it is the favourite filling for home made lace pillows. Oat extract can be used to soothe the skin conditions, e.g. in baths, skin products, etc.

A now obsolete Middle English name for the plant was haver (still used in most other germanic languages), surviving in the name of the livestock feeding bag haversack. In contrast with the names of the other grains, "oat" is usually used in the plural.

Distribution

Top Oats Producers in 2005 (million metric tons)

Russia 5.1

Canada 3.3

United States 1.7

Poland 1.3

Finland 1.2

Australia 1.1

Germany 1.0

Belarus 0.8

China 0.8

Ukraine 0.8

World Total 24.6

Source: ***UN Food & Agriculture Organisation (FAO)***[1]

Oats are native to Eurasia and appear to have been domesticated relatively late. They are now grown throughout the temperate zones. They have a lower summer heat requirement and greater tolerance of rain than other cereals like wheat, rye or barley, so are particularly important in areas with cool, wet summers such as northwest Europe, even being grown successfully in Iceland. Oats are an annual plant, and can be planted either in the fall (for late summer harvest) or in the spring (for early autumn harvest).

Historical attitudes towards oats vary. In England they were considered an inferior grain, because they cannot be made into bread but only "inferior" foods such as porridge or oatcakes, and because they are associated with poorer areas where wheat cannot be grown, with less sun, more rain and less fertile soil, and where as a consequence the people were literally poorer. In Scotland they were, and still are, held in high esteem, as a mainstay of the national diet. A traditional saying in England is that "oats are only fit to be fed to horses and Scotsmen", to which the Scottish riposte is "and England has the finest horses, and Scotland the finest men". Samuel Johnson notoriously defined oats in his Dictionary as "a grain, which in England is generally given to horses, but in Scotland supports the people". While frequently seen as derogatory, this is no less than the literal truth. Oats are so central to traditional Scottish cuisine that the Scottish English word "corn" refers to oats (as opposed to it meaning wheat in England and maize in North America and Australia). Oats grown in Scotland command a premium price throughout the United Kingdom as a result of these traditions.

The discovery of the healthy cholesterol-lowering properties has led to wider appreciation of oats as human food.

Health

Oats are generally considered "healthy", or a health food, being touted commercially as nutritious.

Soluble Fibre

Oat bran is the outer casing of the oat. Its consumption is believed to lower LDL ("bad") cholesterol, and possibly to reduce the risk of heart disease.

After reports found that oats can help lower cholesterol, an "oat bran craze" swept the U.S. in the late 1980s, peaking in 1989, when potato chips with added oat bran were marketed. The food fad was short-lived and faded by the early 1990s. The popularity of oatmeal and other oat products again increased after the January 1998 decision by the Food and Drug Administration (FDA) when it issued its final rule allowing a health claim to be made on the labels of foods containing "soluble fiber" from whole oats (oat bran, oat flour and rolled oats), noting that 3 grams of soluble fiber daily from these foods, in conjunction with a diet low in "saturated fat" and "cholesterol", and "low fat" may reduce the risk of heart disease. In order to qualify for the health claim, the whole oat-containing food must provide at least 0.75 grams of soluble fiber per serving. The soluble fiber in whole oats comprise a class of polysaccharides known as Beta-D-glucan.

Beta-D-glucans, usually referred to as beta-glucans, comprise a class of non-digestible polysaccharides widely found in nature in sources such as grains, barley, yeast, bacteria, algae and mushrooms. In oats, barley and other cereal grains, they are located primarily in the endosperm cell wall.

Oat beta-glucan is a soluble fiber. It is a viscous polysaccharide made up of units of the sugar D-glucose. Oat beta-glucan is comprised of mixed-linkage polysaccharides. This means that the bonds between the D-glucose or D-glucopyranosyl units are either beta-1, 3 linkages or beta-1, 4 linkages. This type of beta-glucan is also referred to as a mixed-linkage (1’3), (1’4)-beta-D-glucan. The (1’3)-linkages break up the uniform structure of the beta-D-glucan molecule and make it soluble and flexible. In comparison, the nondigestible polysaccharide cellulose is also a beta-glucan but is non-soluble. The reason that it is non-soluble is that cellulose consists only of (1’4)-beta-D-linkages. The percentages of beta-glucan in the various whole oat products are: oat bran, greater than 5.5% and up to 23.0%; rolled oats, about 4%; whole oat flour about 4%.

Oats after corn (maize) has the highest lipid content of any cereal, e.g., >10 percent for oats and as high as 17 percent for some maize cultivars compared to about 2-3 percent for wheat and most other cereals. The polar lipid content of oats (about 8-17% glycolipid and 10-20% phospholipid or a total of about 33%) is greater than that of other cereals since much of the lipid fraction is contained within the endosperm.

Protein

Oats

Nutritional value per 100 g

Energy 390 kcal 1630 kJ

Carbohydrates 66 g

- **Dietary fiber** 11 g

Fat 7 g

Protein 17 g

Pantothenic acid (B5) 1.3 mg 26%

Folate (Vit. B9) 56 ¼g 14%

Iron 5 mg 40%

Magnesium 177 mg 48%

²-glucan (soluble fiber) 4 g

Percentages are relative to US RDI values for adults.
Source: ***USDA Nutrient database***

Oat is the only cereal containing a globulin or legume-like protein, avenalins, as the major (80%) storage protein. Globulins are characterized by water solubility; because of this property, oats may be turned into milk but not into bread. The more typical cereal proteins, such as gluten are prolamines. The minor protein of oat is a prolamine: avenin.

Oat protein is nearly equivalent in quality to soy protein which has been shown by the World Health Organization to be the equal to meat, milk, and egg protein. The protein content of the hull-less oat kernel (groat) ranges from 12–24%, the highest among cereals. {Radomir Lasztity. 1999. The chemistry of oats. In: Cereal Chemistry. Akademiai Kiado(English)}

Celiac Disease

Coeliac disease, or celiac disease, from Greek "koiliakos", meaning "suffering in the bowels", is a disease often associated with ingestion of wheat, or more specifically a group of proteins labelled prolamines, or more commonly, gluten.

Oats lack many of the prolamines found in wheat; however, oats do contain avenin[1]. Avenin is a prolamine which is toxic to the intestinal submucosa and can trigger a reaction in some celiacs.[2]

Additionally, oats are frequently processed near wheat, barley and other grains such that they become contaminated with other glutens. Because of this, the FAO:n Codex Alimentarius Commission officially lists them as a crop containing gluten. Oats from Ireland and Scotland, where less wheat is grown, are less likely to be contaminated in this way.

Oats are part of a gluten free diet in, for example, Finland and Sweden. In both of these countries there are "pure oat" products on the market.

Agronomy

Oats are sown in the spring, as soon as the soil can be worked. An early start is crucial to good yields as oats will go dormant during the summer heat. Oats are cold-tolerant and will be unaffected by late frosts or snow. Typically about 100 kg/hectare (about 2 bushels per acre) are sown, either broadcast or drilled in 150 mm (6 inch) rows. Lower rates are used when underseeding with a legume. Somewhat higher rates can be used on the best soils. Excessive sowing rates will lead to problems with lodging and may reduce yields.

Winter oats may be grown as an off-season groundcover and plowed under in the spring as a green fertilizer.

Oats remove substantial amounts of nitrogen from the soil. If the straw is removed from the soil rather than being ploughed back, there will also be removal of large quantities of potash. Usually 50-100 kg/hectare (50-100 pounds per acre) of nitrogen in the form of urea or ammonium sulphate is sufficient. A sufficient amount of nitrogen is particularly important for plant height and hence straw quality and yield. When the prior-year crop was a legume, or where ample manure is applied, nitrogen rates can be reduced somewhat.

The vigorous growth habit of oats will tend to choke out most weeds. A few tall broadleaf weeds, such as ragweed, goosegrass and buttonweed (velvetleaf), can occasionally be a problem as they complicate harvest. These can be controlled with a modest application of a broadleaf herbicide such as 2,4-D while the weeds are still small.

Modern harvest technique is a matter of available equipment, local tradition, and priorities. Best yields are attained by swathing, cutting the plants at about 10 cm (4 inches) above ground and putting them into windrows with the grain all oriented the same way, just before the grain is completely ripe. The windrows are left to dry in the sun for several days before being combined using a dummy head. Then the straw is baled.

Oats can also be left standing until completely ripe and then combined with a grain head. This will lead to greater field losses as the grain falls from the heads and to harvesting losses as the grain is threshed out by the reel. Without a draper head, there will also be somewhat more damage to the straw since it will not be properly oriented as it enters the throat of the combine. Overall yield loss is 10-15% compared to proper swathing.

Late 19th and early 20th century harvesting was performed using a binder. Oats were gathered into shocks and then collected and run through a stationary threshing machine.

Earlier harvest involved cutting with a scythe or sickle, and threshing under the feet of cattle.

A good yield is typically about 3000 kg/hectare (100 bushels/acre) of grain and two tonnes of straw.

Trivia

- The eruption of Mount Tambora caused a change in world climate resulting in a volcanic winter and the "year without a summer" in 1816, during which time the price of oats rose dramatically, for example in the USA from 12 to 92 cents per bushel. This led to the starvation of many horses, which in turn led

to transportation problems, which Baron Karl von Drais attempted to solve by inventing the dandy horse, the direct precursor to the bicycle.

- Bodybuilders may be known to eat copious amounts of oats to get adequate carbohydrate.

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Peppermint

Scientific classification

Kingdom: Plantae
Division: Magnoliophyta
Class: Magnoliopsida
Order: Lamiales
Family: Lamiaceae
Genus: Mentha

Binomial name Mentha × piperita

Peppermint (Mentha × piperita) is a (usually) sterile hybrid mint, a cross between watermint (Mentha aquatica) and spearmint (Mentha spicata). It is occasionally found wild with its parent species in central and southern Europe, but the first intentional crossbreed of watermint and spearmint was done in England. Being sterile, it spreads by rooting.

The stems are from 30-70 cm tall, rarely up to 100 cm, smooth, and square in cross section. The leaves are from 4-9 cm long and 1.5-4 cm broad, dark green with reddish veins, and with an acute apex and coarsely toothed margins. The flowers are purple, 6-8 mm long, with a four-lobed corolla about 5 mm diameter; they are produced in whorls around the stem, forming thick, blunt spikes. Flowering is from July to September.

Peppermint is generally regarded as 'the world's oldest medicine', with archeological evidence placing its use at least as far back as ten thousand years ago.

Uses

Peppermint has a high menthol content, and is often used as a flavouring in tea, ice cream, confectionery, chewing gum, and toothpaste. The oil also contains menthone and menthyl esters. It is the oldest and most popular flavour of mint-flavored confectionery. Peppermint

can also be found in some shampoos and soaps, which give the hair a minty scent and produce a cooling sensation on the skin.

Peppermint, like many spices and herbs, is believed to have medicinal properties when consumed. It is said that it helps against upset stomachs, inhibits the growth of certain bacteria, and can help smooth and relax muscles when inhaled or applied to the skin. Other health benefits are attributed to the high manganese, vitamin C and vitamin A content; as well as trace amounts of various other nutrients such as fibre, iron, calcium, folate, potassium, tryptophan, magnesium, omega-3 fatty acids, riboflavin, and copper.

Peppermint oil has been demonstrated to reduce colicky abdominal pain due to irritable bowel syndrome (IBS) with an NNT (number needed to treat) around 3.1[1], but the oil is irritant to the stomach in the quantity required and therefore needs wrapping for delayed release in the intestine. Peppermint relaxes the gastro-oesophageal sphincter, thus promoting belching.

Peppermint flowers are heavy nectar producers and honeybees as well as other nectar harvesting organisms forage them heavily. A mild, pleasant varietal honey can be produced if there is sufficient acreage of plants.

Areas of North America where peppermint was formerly grown for oil (now produced synthetically) often have an abundance of feral plants, and it is considered somewhat invasive.

Cultivation

Peppermint generally thrives in shade and expands quickly by underground rhizomes. If you choose to grow peppermint, it is advisable to plant it in a container, otherwise it can rapidly take over a whole garden. It needs a good water supply, and is ideal for planting in part-sun to shade areas.

The leaves and flowering tops, collected as soon as the flowers begin to open and carefully dried, are the useable portion of the plant. The wild form of the plant is less suitable for this purpose, with cultivated plants having been selected for more and better oil content. Peppermint grows from the ground.

Reference

1. ^ http://www.jr2.ox.ac.uk/bandolier/booth/alternat/AT022.html

Rosemary

Conservation status: Secure

Scientific classification

Kingdom: Plantae
Division: Magnoliophyta
Class: Magnoliopsida
Order: Lamiales
Family: Lamiaceae
Genus: Rosmarinus
Species: *R. officinalis*

Binomial name Rosmarinus officinalis

Rosemary (Rosmarinus officinalis) is a woody, perennial herb with fragrant evergreen needle-like leaves. It is native to the Mediterranean region. It is a member of the mint family Lamiaceae, which also includes many other herbs. Forms range from upright to trailing; the upright forms can reach 1.5 m tall, rarely 2 m. The leaves are evergreen, 2-4 cm long and 2-5 mm broad, green above, and white below with dense short woolly hairs. The flowers are variable in colour, being white, pink, purple, or blue.

The name rosemary has nothing to do with the rose or the name Mary, but derives from the Latin name rosmarinus, which is presumed to mean "dew of the sea", though some think this too may be derived from an earlier name.

Rosemary is often commonly associated with memory and/or remembrance of the past.

Cultivation and uses

The fresh and dried leaves are used frequently in traditional Mediterranean cuisine as a herb; a tisane can also be made from them. They are extensively used in cooking, and when burned gives off a distinct mustard smell.

Since it is attractive and tolerates some degree of drought, it is also used in landscaping, especially in areas having a Mediterranean climate. It can in fact die in over-watered soil, but is otherwise quite easy to grow for beginner gardeners. It is very pest-resistant.

Rosemary is easily pruned into shapes and has been used for topiary. When grown in pots, it is best kept trimmed to stop it getting too straggly and unsightly, though when grown in a garden, rosemary can grow quite large and still be attractive. It can be propagated from an existing plant by clipping a shoot 10-15 cm long, stripping a few leaves from the bottom, and planting it directly into soil.

Numerous cultivars have been selected for garden use. The following are frequently sold:

- 'Albus': white flowers
- 'Arp': leaves light green, lemon-scented
- 'Aureus': leaves speckled yellow
- 'Benenden Blue': leaves narrow, dark green
- 'Blue Boy': dwarf, small leaves
- 'Golden Rain': leaves green, with yellow streaks
- 'Irene': lax, trailing
- 'Lockwood de Forest': procumbent selection from 'Tuscan Blue'
- 'Ken Taylor': shrubby
- 'Majorica Pink': pink flowers

- 'Miss Jessop's Upright': tall, erect
- 'Pinkie': pink flowers
- 'Prostratus'
- 'Pyramidalis' (a.k.a 'Erectus'): pale blue flowers
- 'Roseus': pink flowers
- 'Severn Sea': spreading, with arching branches; flowers deep violet
- 'Tuscan Blue': upright

Rosemary is a useful food preservative, according to research published in 1987 by Rutgers University, New Jersey. Researchers at Rutgers patented a chemical derived from rosemary that compares favourably with BHA and BHT in its preservative properties.

Rosemary can be added as an unusual extra flavouring in lemonade.

Medicinal uses

Rosemary has been found to be a stimulant and mild analgesic, and has been used to treat headaches, poor circulation, and many ailments for which stimulants are prescribed.

Rosemary essential oil is a powerful convulsant; if applied to the skin, it may cause seizures in otherwise healthy adults or children.

It can be used as a disinfectant, as a mouth wash and to treat fever or rheumatism.

Externally it can be used in hair lotions; a few drops of Rosemary oil massaged into the scalp, then rinsed with an infusion of nettles can revitalise the hair. Used in this manner it supposed to prevent premature baldness. Rosemary is also reported to stop dandruff.

Hungary water was first invented for a Queen of Hungary to 'renovate vitality of paralysed limbs'. It was used externally and is prepared by mixing 180g of fresh rosemary tops in full flower into a litre of spirits of wine. Leave to stand for four days then distill. It is also supposed to work as a remedy against gout if rubbed vigoursly on hands and feet.

For a tonic against headaches put some sprigs into a teapot, add hot water, strain, and serve.

Rosemary has a very old reputation for improving memory, and has been used as a symbol for remembrance (as in worn during weddings, war commemorations and funerals) in Europe, probably as a result of this reputation; in Shakespeare's Hamlet, Ophelia says, "There's rosemary, that's for remembrance".

Rosemary and its constituents carnosol and ursolic acid have been shown to inhibit the growth of skin tumors and to provide a natural anti-oxidant protection against skin cancer and photodamage.

Don Quixote (Chapter XVII, 1st volume) mixes it in its recipe of the miraculous balm of Fierabras with revolting results.

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Saffron

Saffron crocus

Scientific classification

Kingdom: Plantae
Division: Magnoliophyta
Class: Liliopsida
Order: Asparagales
Family: Iridaceae
Genus: Crocus
Species: *C. sativus*

Binomial name *Crocus sativus*

Saffron (IPA: [Èsæf.yYn] / [Èsæf.yTn]) is a spice derived from the flower of the *saffron crocus* (Crocus sativus), a species of crocus in the family Iridaceae. The flower has three stigmas, which are the distal ends of the plant's carpels. Together with its style, the stalk connecting the stigmas to the rest of the plant, these components are often dried and used in cooking as a seasoning and colouring agent. Saffron, which has for decades been the world's most expensive spice by weight,[1][2] is native to Southwest Asia.[2][3] It was first cultivated in the vicinity of Greece.[4]

Saffron is characterised by a bitter taste and an iodoform- or hay-like fragrance; these are caused by the chemicals picrocrocin and safranal.[5][6] It also contains a carotenoid dye, crocin, that gives food a rich golden-yellow hue. These traits make saffron a much-sought ingredient in many foods worldwide. Saffron also has medicinal applications.

The word saffron originated from the 12th-century Old French term safran, which derives from the Latin word safranum. Safranum is also related to the Italian zafferano and Spanish azafrán.[7] Safranum comes from the Arabic word acfar (#N5RAN1), which means "yellow," via the paronymous za»farn (2N9RAN1N'F), the name of the spice in Arabic.[6]

Biology

Saffron crocus morphology

The domesticated saffron crocus C. sativus is a fall-flowering perennial plant unknown in the wild, and is a sterile triploid mutant of the eastern Mediterranean fall-flowering Crocus cartwrightianus.[8] According to botanical research, C. cartwrightianus originated in Crete,

not—as was once generally believed—in Central Asia.[6] The saffron crocus resulted when C. cartwrightianus was subjected to extensive artificial selection by growers who desired elongated stigmas. Being sterile, the saffron crocus's purple flowers fail to produce viable seeds—thus, reproduction is dependent on human assistance: the corms (underground bulb-like starch-storing organs) must be manually dug up, broken apart, and replanted. A corm survives for only one season, reproducing via division into up to ten "cormlets" that eventually give rise to new plants.[8] The corms are small brown globules up to 4.5 cm in diameter and are shrouded in a dense mat of parallel fibers.

After a period of aestivation in summer, five to eleven narrow and nearly vertical green leaves—growing up to 40 cm in length—emerge from the ground. In autumn, purple buds appear. Only in October, after most other flowering plants have released their seeds, does it develop its brilliantly-hued flowers, ranging from a light pastel shade of lilac to a darker and more striated mauve.[9] Upon flowering, it averages less than 30 cm in height.[10] Inside each flower is a three-pronged style; in turn, each prong terminates with a crimson stigma 25–30 mm in length.[8]

Cultivation

The saffron crocus thrives in climates similar to that of the Mediterranean maquis or the North American chaparral, where hot, dry summer breezes blow across arid and semi-arid lands. Nevertheless, the plant can tolerate cold winters, surviving frosts as cold as 10°C and short periods of snow cover.[11][8] However, if not grown in wet environments like Kashmir (where rainfall averages 1000–1500 mm annually), irrigation is needed—this is true in the saffron-growing regions of Greece (500 mm of rainfall annually) and Spain (400 mm). Rainfall timing is also key: generous spring rains followed by relatively dry summers are optimal. In addition, rainfall occurring immediately prior to flowering also boosts saffron yields; nevertheless, rainy or cold weather occurring during flowering promotes disease, thereby reducing yields. Persistently damp and hot conditions also harm yields,[12] as do the digging actions of rabbits, rats, and birds. Parasites such as nematodes, leaf rusts, and corm rot also pose significant threats.[13]

Saffron crocus flower yields[*]

Country, Yield (kg/ha)

Spain 6–29

Italy 10–16

Greece 4–7

India 2–7

Morocco 2.0–2.5

Source: Deo 2003, p. 3

[*]—Yields specify flower weight, not final dry saffron weight.

Saffron plants grow best in strong and direct sunlight, and fare poorly in shady conditions. Thus, planting is best done in fields that slope towards the sunlight (i.e. south-sloping in the Northern Hemisphere), maximizing the crocuses' sun exposure. In the Northern Hemisphere, planting is mostly done in June, with corms planted some 7–15 cm deep. Planting depth and corm spacing—along with climate—are both critical factors impacting plant yields. Thus, mother corms planted more deeply yield higher-quality saffron, although they produce fewer flower buds and daughter corms. With such knowledge, Italian growers have found that planting corms 15 cm deep and in rows spaced 2–3 cm apart optimizes threads yields, whereas planting depths of 8–10 cm optimizes flower and corm production. Meanwhile, Greek, Moroccan, and Spanish growers have devised different depths and spacings to suit their own climates.[12]

Saffron crocuses grow best in friable, loose, low-density, well-watered, and well-drained clay-calcareous soils with high organic content. Raised beds are traditionally used to promote good drainage. Historically, soil organic content was boosted via application of some 20–30 tonnes of manure per hectare. Afterwards—and with no further manure application—corms were planted.[13] After a period of dormancy through the summer, the corms send up their narrow leaves and begin to bud in early autumn. Only in mid-autumn do the plants begin to flower. Harvesting of flowers is by necessity a speedy affair: after their flowering at dawn, flowers quickly wilt as the day passes.[14] Furthermore, saffron crocuses bloom within a narrow window spanning one or two weeks.[15] Approximately 150 flowers yield 1 g of dry saffron threads; to produce 12 g of dried saffron (72 g freshly harvested), 1 kg of flowers are needed. On average, one freshly-picked flower yields 0.03 g of fresh saffron, or 0.007 g of dried saffron.[13]

Chemistry

Crocin formation
Esterification reaction between crocetin and gentiobiose.

— ²-D-gentiobiose.

— Crocetin.

Picrocrocin and safranal

Chemical structure of picrocrocin.[16]

— Safranal moiety.

— ²-D-glucopyranose derivative.

Saffron contains more than 150 volatile and aroma-yielding compounds. It also has many nonvolatile active components,[17] many of which are carotenoids, including zeaxanthin, lycopene, and various ±- and ²-carotenes. However, saffron's golden yellow-orange colour is

primarily the result of ±-crocin. This crocin is trans-crocetin di-(²-D-gentiobiosyl) ester (systematic (IUPAC) name: 8,8-diapo-8,8-carotenoic acid). This means that the crocin underlying saffron's aroma is a digentiobiose ester of the carotenoid crocetin.[17] Crocins themselves are a series of hydrophilic carotenoids that are either monoglycosyl or diglycosyl polyene esters of crocetin.[17] Meanwhile, crocetin is a conjugated polyene dicarboxylic acid that is hydrophobic, and thus oil-soluble. When crocetin is esterified with two water-soluble gentiobioses (which are sugars), a product results that is itself water-soluble. The resultant ±-crocin is a carotenoid pigment that may comprise more than 10% of dry saffron's mass. The two esterified gentiobioses make ±-crocin ideal for colouring water-based (non-fatty) foods such as rice dishes.[4]

Chemical composition of saffron

Component - Mass %

carbohydrates 12.0–15.0

water 9.0–14.0

polypeptides 11.0–13.0

cellulose 4.0–7.0

lipids 3.0–8.0

minerals 1.0–1.5

miscellaneous non-nitrogenous 40.0

Source: Dharmananda 2005

Proximate analysis of saffron

Component - Mass %

Water-soluble components 53.0

’ Gums 10.0

’ Pentosans 8.0

’ Pectins 6.0

’ Starch 6.0

’ ±–Crocin 2.0

’ Other carotenoids 1.0

Lipids 12.0

’ Non-volatile oils 6.0

’ Volatile oils 1.0

Protein 12.0

Inorganic matter ("ash") 6.0

’ HCl-soluble ash 0.5

Water 10.0

Fiber (crude) 5.0

Source: Goyns 1999, p. 46

The bitter glucoside picrocrocin is responsible for saffron's flavour. Picrocrocin (chemical formula: C16H26O7; systematic name: 4-(²-D-glucopyranosyloxy)-2,6,6-trimethylcyclohex-1-ene-1-carboxaldehyde) is a union of an aldehyde sub-element known as safranal (systematic name: 2,6,6-trimethylcyclohexa-1,3-dien-1- carboxaldehyde) and a carbohydrate. It has insecticidal and pesticidal properties, and may comprise up to 4% of dry saffron. Significantly, picrocrocin is a truncated version (produced via oxidative cleavage) of the carotenoid zeaxanthin and is the glycoside of the terpene aldehyde safranal. The reddish-coloured[18] zeaxanthin is, incidentally, one of the carotenoids naturally present within the retina of the human eye.

When saffron is dried after its harvest, the heat, combined with enzymatic action, splits picrocrocin to yield D-glucose and a free safranal molecule.[16] Safranal, a volatile oil, gives saffron much of its distinctive aroma.[5][19] Safranal is less bitter than picrocrocin and may comprise up to 70% of dry saffron's volatile fraction in some samples.[18] A second element underlying saffron's aroma is 2-hydroxy-4,4,6-trimethyl-2,5-cyclohexadien-1-one, the scent of which has been described as "saffron, dried hay like".[20] Chemists found this to be the most powerful contributor to saffron's fragrance despite its being present in a lesser quantity than safranal.[20] Dry saffron is highly sensitive to fluctuating pH levels, and rapidly breaks down chemically in the presence of light and oxidizing agents. It must therefore be stored away in air-tight containers in order to minimise contact with atmospheric oxygen. Saffron is somewhat more resistant to heat.

History

The history of saffron cultivation reaches back more than 3,000 years.[8] The wild precursor of domesticated saffron crocus was Crocus cartwrightianus. Human cultivators bred wild specimens by selecting for unusually long stigmas. Thus, a sterile mutant form of C. cartwrightianus, C. sativus, emerged in late Bronze Age Crete.[21] Experts believe saffron was first documented in a 7th century BC Assyrian botanical reference compiled under

Ashurbanipal. Since then, documentation of saffron's use over the span of 4,000 years in the treatment of some 90 illnesses has been uncovered.[22] Saffron has been used as a spice and medicine in the Mediterranean region since then, with usage and cultivation slowly spreading to other parts of Eurasia as well as North Africa and North America. In the last several decades, saffron cultivation has spread to Oceania.

Mediterranean

Minoans portrayed saffron in their palace frescoes by 1500–1600 BC, showing saffron's use as a therapeutic drug.[23][22] Later, Greek legends told of sea voyages to Cilicia. There, adventurers hoped to procure what they believed was the world's most valuable saffron.[11] Another legend tells of Crocus and Smilax, whereby Crocus is bewitched and transformed into the original saffron crocus.[24] Ancient Mediterranean peoples—including perfumers in Egypt, physicians in Gaza, townspeople in Rhodes,[25] and the Greek hetaerae courtesans—used saffron in their perfumes, ointments,[26] potpourris, mascaras, divine offerings, and medical treatments.[26]

In late Hellenistic Egypt, Cleopatra used saffron in her baths so that lovemaking would be more pleasurable.[27] Egyptian healers used saffron as a treatment for all varieties of gastrointestinal ailments.[28] Saffron was also used as a fabric dye in such Levant cities as Sidon and Tyre.[29] Such was the Romans' love of saffron that Roman colonists took their saffron with them when they settled in southern Gaul, where it was extensively cultivated until Rome's fall. Competing theories state that saffron only returned to France with 8th century AD Moors or with the Avignon papacy in the 14th century AD.[30]

Asia The 17.8 m monolith of Jain God Bhagavan Gomateshwara Bahubali, which was carved between 978–993 AD and is located in Shravanabelagola, India, is anointed with saffron every 12 years by thousands of devotees as part of the Mahamastakabhisheka festival.

Saffron-based pigments have been found in 50,000 year-old depictions of prehistoric beasts in what is today Iraq.[24][31] Later, the Sumerians used wild-growing saffron in their remedies and magical potions.[32] Saffron was thus an article of long-distance trade before the Minoan palace culture's 2nd millennium BC peak. Saffron was also honored in the Hebrew Song of Solomon.[33] Ancient Persians cultivated Persian saffron (Crocus sativus 'Hausknechtii') in Derbena, Isfahan, and Khorasan by the 10th century BC. At such sites, saffron threads were woven into textiles,[24] ritually offered to divinities, and used in dyes, perfumes, medicines, and body washes.[34] Thus, saffron threads would be scattered across beds and mixed into hot teas as a curative for bouts of melancholy. Non-Persians also feared the Persians' usage of saffron as a drugging agent and aphrodisiac.[26] During his Asian campaigns, Alexander the Great used Persian saffron in his infusions, rice, and baths as a curative for battle wounds. Alexander's troops mimicked the practice and brought saffron-bathing back to Greece.[35]

Theories explaining saffron's arrival in South Asia conflict. Traditional Kashmiri and Chinese accounts date its arrival anywhere between 900–2500 years ago.[36][37][38]

Meanwhile, historians studying ancient Persian records date the arrival to sometime prior to 500 BC,[4] attributing it to either Persian transplantation of saffron corms to stock new gardens and parks[39] or to a Persian invasion and colonization of Kashmir. Phoenicians then marketed Kashmiri saffron as a dye and a treatment for melancholy.[26] From there, saffron use in foods and dyes spread throughout South Asia. For example, Buddhist monks in India adopted saffron-coloured robes after the Buddha Siddhartha Gautama's death.[40]

Historians believe that saffron first came to China with Mongol invaders by way of Persia. Yet a 7th-century Armenian author, Anania of Shirak, observed in his description of China that "unlimited amounts of saffron are available there, to the point that if someone went hunting, dressed in white, mounted on a white horse and with a white falcon, on his return he would be completely covered with yellow"[1]. Indeed, saffron is mentioned in ancient Chinese medical texts, including the forty-volume Shennong Bencaojing (^²,I“ — "Shennong's Great Herbal", also known as Pen Ts'ao or Pun Tsao) pharmacopoeia, a tome dating from 200-300 BC. Traditionally attributed to the legendary Yan ("Fire") Emperor (Ž) Shennong, it documents 252 phytochemical-based medical treatments for various disorders.[41][42][40] Yet around the 3rd century AD, the Chinese were referring to saffron as having a Kashmiri provenance. For example, Wan Zhen, a Chinese medical expert, reported that "[t]he habitat of saffron is in Kashmir, where people grow it principally to offer it to the Buddha." Wan also reflected on how saffron was used in his time: "The [saffron crocus] flower withers after a few days, and then the saffron is obtained. It is valued for its uniform yellow colour. It can be used to aromatise wine."[38]

Europe

In Europe, saffron cultivation declined steeply following the Roman Empire's fall. Saffron was reintroduced when Moorish civilization spread to Spain, France, and Italy.[43] During the 14th century Black Death, demand for saffron-based medicine skyrocketed, and much saffron had to be imported via Venetian and Genoan ships from southern and Mediterranean lands[44] such as Rhodes. The theft of one such shipment by noblemen sparked the fourteen-week long "Saffron War".[44] The conflict and resulting fear of rampant saffron piracy spurred significant saffron cultivation in Basel, which grew prosperous.[45] Cultivation and trade then spread to Nuremberg, where epidemic levels of saffron adulteration brought on the Safranschou code, which fined, imprisoned, and executed saffron adulterers.[46] Soon after, saffron cultivation spread throughout England, especially Norfolk and Suffolk. The Essex town of Saffron Walden, named for its new specialty crop, emerged as England's prime saffron growing and trading center. However, an influx of more exotic spices—chocolate, coffee, tea, and vanilla—from newly-contacted Eastern and overseas countries caused European cultivation and usage of saffron to decline.[47][48] Only in southern France, Italy, and Spain, did significant cultivation endure.[49]

Europeans brought saffron to the Americas when immigrant members of the Schwenkfelder Church left Europe with a trunk containing saffron corms; indeed, many Schwenkfelders had widely grown saffron in Europe.[50] By 1730, the Pennsylvania Dutch were cultivating saffron throughout eastern Pennsylvania. Spanish colonies in the Caribbean bought large amounts of this new American saffron, and high demand ensured that saffron's

list price on the Philadelphia commodities exchange was set equal to that of gold.[51] The trade with the Caribbean later collapsed in the aftermath of the War of 1812, when many saffron-transporting merchant vessels were destroyed.[52] Yet the Pennsylvania Dutch continued to grow lesser amounts of saffron for local trade and use in their cakes, noodles, and chicken or trout dishes.[53] American saffron cultivation survived into modern times mainly in Lancaster County, Pennsylvania.[50]

Trade and usage

Saffron's aroma is often described by connoisseurs as reminiscent of metallic honey with grassy or hay-like notes, while its taste has been noted also as hay-like and somewhat bitter. Saffron also contributes a luminous yellow-orange colouring to foods. Because of the unusual taste and colouring it adds to foods, saffron is widely used in Arab, Central Asian, European, Indian, Iranian, Moroccan and Cornish cuisines. Confectionaries and liquors also often include saffron. Common saffron substitutes include safflower (Carthamus tinctorius, which is often sold as "Portuguese saffron" or "assafroa") and turmeric (Curcuma longa). Medicinally, saffron has a long history as part of traditional healing; modern medicine has also discovered saffron as having anticarcinogenic (cancer-suppressing),[17] anti-mutagenic (mutation-preventing), immunomodulating, and antioxidant-like properties.[54][17][55] Saffron has also been used as a fabric dye—particularly in China and India—and in perfumery.[56]

Most saffron is grown in a belt of land ranging from the Mediterranean in the west to Kashmir in the east. Annually, around 300 tonnes of saffron are produced worldwide.[6] Iran, Spain, India, Greece, Azerbaijan, Morocco, and Italy (in decreasing order of production) are the major producers of saffron. A pound of dry saffron (0.45 kg) requires 50,000–75,000 flowers, the equivalent of a football field's area of cultivation.[57][58] Some forty hours of frenetic day-and-night labour are needed to pick 150,000 flowers.[59] Upon extraction, stigmas are dried quickly and (preferably) sealed in airtight containers.[60] Saffron prices at wholesale and retail rates range from US$500/pound to US$5,000/pound (US$1100–US$11,000 per kilogram). In Western countries, the average retail price is $1,000/pound (US$2200 per kilogram).[2] Between 70,000 and 200,000 threads comprise a pound. Vivid crimson colouring, slight moistness, elasticity, recent harvest date, and lack of broken-off thread debris are all traits of fresh saffron.

Cultivars

Several saffron cultivars are grown worldwide. Spain's varieties, including the tradenames 'Spanish Superior' and 'Creme', are generally mellower in colour, flavour, and aroma; they are graded by government-imposed standards. Italian varieties are more potent, while the most intense varieties tend to be Macedonian Greek, Iranian, and Kashmiri Indian in origin. Westerners may face significant obstacles in obtaining saffron from Iran and India. For example, the United States has banned the import of Iranian saffron; meanwhile, India has banned the export of high-grade saffron abroad. Aside from these, various "boutique" crops are available from New Zealand, France, Switzerland, England, the United States, and

other countries. In the U.S., Pennsylvania Dutch saffron — known for its earthy notes — is marketed in small quantities.[50][61]

Consumers regard certain cultivars as "premium" quality. The "Aquila" saffron (zafferano dell'Aquila) — defined by high safranal and crocin content, shape, unusually pungent aroma, and intense colour — is grown exclusively on eight hectares in the Navelli Valley of Italy's Abruzzo region, near L'Aquila. It was first introduced to Italy by a Dominican monk from Inquisition-era Spain. But in Italy the biggest saffron cultivation, for quality and quantity, is in San Gavino Monreale, Sardinia. There, saffron is grown on 40 hectares (60% of Italian production); it also has very high crocin, picrocrocin, and safranal content. Another is the Kashmiri "Mongra" or "Lacha" saffron (Crocus sativus 'Cashmirianus'), which is among the most difficult for consumers to obtain. Repeated droughts, blights, and crop failures in Kashmir, combined with an Indian export ban, contribute to its high prices. Kashmiri saffron is recognisable by its extremely dark maroon-purple hue, among the world's darkest, which suggests the saffron's strong flavour, aroma, and colourative effect.

Grades

Minimum saffron colour grading standards (ISO 3632)

ISO Grade (category) - Crocin-specific absorbance (A**»**) score (at »=440 nm)

I > 190

II 150–190

III 110–150

IV 80–110

Source: Tarvand 2005b

Saffron types are graded by quality according to laboratory measurements of such characteristics as crocin (colour), picrocrocin (taste), and safranal (fragrance) content. Other metrics include floral waste content (i.e. the saffron spice sample's non-stigma floral content) and measurements of other extraneous matter such as inorganic material ("ash"). A uniform set of international standards in saffron grading was established by the International Organization for Standardization, which is an international federation of national standards bodies. Namely, ISO 3632 deals exclusively with saffron. It establishes four empirical grades of colour intensity: IV (poorest), III, II, and I (finest quality). Saffron samples are then assigned to one of these grades by gauging the spice's crocin content, which is revealed by measurements of crocin-specific spectroscopic absorbance. Absorbance is defined as A**»** = log(I / I***0***), with A**»** as absorbance. It is a measure of a given substance's transparency (I / I***0***, the ratio of light intensity passing through sample to that of the incident light) to a given wavelength of light.

For saffron, absorbance is determined for the crocin-specific photon wavelength of 440 nm in a given dry sample of spice.[62] Higher absorbances at this wavelength imply greater

crocin concentration, and thus a greater colourative intensity. These data are measured through photospectroscopy reports at certified testing laboratories worldwide. These colour grades proceed from grades with absorbances lower than 80 (for all category IV saffron) up to 190 or greater (for category I). The world's finest samples (the selected most red-maroon tips of stigmas picked from the finest flowers) receive absorbance scores in excess of 250. Market prices for saffron types follow directly from these ISO scores.[62] However, many growers, traders, and consumers reject such lab test numbers. They prefer a more holistic method of sampling batches of thread for taste, aroma, pliability, and other traits in a fashion similar to that practiced by practised wine tasters.[63]

Spanish federal saffron grading standards

Grade - ISO score

Coupe > 190

La Mancha 180–190

Rio 150–180

Standard 145–150

Sierra < 110

Source: Tarvand 2005b

Despite such attempts at quality control and standardisation, an extensive history of saffron adulteration—particularly among the cheapest grades—continues into modern times. Adulteration was first documented in Europe's Middle Ages, when those found selling adulterated saffron were executed under the Safranschou code.[64] Typical methods include mixing in extraneous substances like beet, pomegranate fibers, red-dyed silk fibers, or the saffron crocus's tasteless and odorless yellow stamens. Other methods included dousing saffron fibers with viscid substances like honey or vegetable oil. However, powdered saffron is more prone to adulteration, with turmeric, paprika, and other powders used as diluting fillers. Adulteration can also consist of selling mislabeled mixes of different saffron grades.[40] Thus, in India, high-grade Kashmiri saffron is often sold mixed with cheaper Iranian imports; these mixes are then marketed as pure Kashmiri saffron, a development that has cost Kashmiri growers much of their income.[65][66]

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Sassafras

Scientific classification

Kingdom: Plantae
Division: Magnoliophyta
Class: Magnoliopsida
Order: Laurales
Family: Lauraceae
Genus: *Sassafras*

Species

Sassafras albidum
Sassafras tzumu

Sassafras is a genus of two species of deciduous trees in the family Lauraceae, native to eastern North America and eastern Asia.

Sassafras trees grow from 15-35 m tall and 70-150 cm diameter, with many slender branches, and smooth, orange-brown bark. The branching is sympodial. The bark of the mature trunk is thick, red-brown, and deeply furrowed. The wood is light, soft, weak, and brittle. All parts of the plants are very fragrant.

The species are unusual in having three distinct leaf patterns on the same plant; unlobed oval, bilobed (mitten-shaped), and trilobed (three pronged). They have smooth margins and grow 7-20 cm long by 5-10 cm broad. The young leaves and twigs are quite mucilaginous. The tiny, yellow flowers are five-petaled and bloom in the spring; they are dioecious, with male and female flowers on separate trees. The fruit are blue-black, egg-shaped, 1 cm long, produced on long, red-stalked cups, and mature in late summer.

The name "Sassafras", applied by the Spanish botanist Nicolas Monardes in the sixteenth century, is said to be a corruption of the Spanish word for saxifrage. It was also called "pauame" by Native Americans.

Species

- Sassafras albidum (Nuttall) Nees - *Sassafras*, *White Sassafras*, *Red Sassafras* or *Silky Sassafras*. Eastern North America, from southernmost Ontario, Canada through the eastern United States south to central Florida, and west to southern Iowa and eastern Texas.
- Sassafras tzumu (Hemsl.) Hemsl. - *Chinese Sassafras* or *Tzumu*. Central and southwestern China. It differs from S. albidum in the leaves being more frequently three-lobed, the lobes having a tapered acuminate apex (not rounded to weakly acute).
- Sassafras randaiense (Hayata) Rehd. - *Taiwan Sassafras*. Taiwan, regarded synonym of Yushunia randaiensis (Hayata) Kamikoti.

Uses

Essential oil distilled from the root-bark or the fruit was used as a fragrance in perfumes and soaps, food (sassafras tea and candy flavoring) and for aromatherapy. It is also used as a pain killer as well as an antiseptic in dentistry.The smell of sassafras oil is said to make an excellent repellent for mosquitoes and other insects, which makes it a nice yard plant. The root or root bark is also used to make tea. A yellow dye is obtained from the wood. The shoots are used to make root beer (formerly an alcoholic beverage, but now a soft drink), which owes its characteristic odor to the sassafras extract. The leaves are used for thickening sauces and soups, and when dried and ground are known as filé powder, a spice used in Cajun, Creole, and other Louisiana cooking, such as the dish filé gumbo. The pith is used in the U.S. to soothe eye inflammation and ease catarrh.Acids can be extracted from bark for manufacturing perfumes.

Safrole, which is the main component (75-80%) of sassafras essential oil, is now recognized by the United States Department of Agriculture as a potential carcinogen. Sassafras oil is also the preferred source of safrole for MDMA production by clandestine laboratories, thus its sale is monitored by the U.S. Drug Enforcement Administration.

Willow

Scientific classification

Kingdom: Plantae
Division: Magnoliophyta
Class: Magnoliopsida
Order: Malpighiales
Family: Salicaceae
Genus: *Salix* L.

Species

About 350, including:
Salix acutifolia - Violet Willow
Salix alaxensis - Alaska Willow
Salix alba - White Willow
Salix alpina - Alpine Willow
Salix amygdaloides - Peachleaf Willow
Salix arbuscula - Mountain Willow
Salix arbusculoides - Littletree Willow
Salix arctica - Arctic Willow
Salix atrocinerea
Salix aurita - Eared Willow
Salix babylonica - Peking Willow
Salix bakko
Salix barrattiana - Barratt's Willow

Salix bebbiana - Beaked Willow
Salix boothii - Booth Willow
Salix bouffordii
Salix brachycarpa - Barren-ground Willow
Salix cacuminis
Salix canariensis
Salix candida - Sage Willow
Salix caprea - Goat Willow
Salix caroliniana - Coastal Plain Willow
Salix chaenomeloides
Salix chilensis
Salix cinerea - Grey Sallow
Salix cordata
Salix daphnoides
Salix discolor - Pussy Willow
Salix eastwoodiae - Eastwood's Willow
Salix eleagnos
Salix eriocarpa
Salix eriocephala - Heartleaf Willow
Salix exigua - Sandbar Willow
Salix foetida
Salix fragilis - Crack Willow
Salix futura
Salix geyeriana
Salix gilgiana
Salix glauca
Salix gooddingii - Goodding Willow
Salix gracilistyla
Salix hainanica - Hainan Willow
Salix helvetica - Swiss Willow
Salix herbacea - Dwarf Willow
Salix hookeriana - Hooker's Willow
Salix hultenii
Salix humboldtiana - Chile Willow
Salix humilis - Upland Willow
Salix integra
Salix interior
Salix japonica
Salix jessoensis
Salix koriyanagi
Salix kusanoi
Salix lanata - Woolly Willow
Salix lapponum - Downy Willow
Salix lasiandra - Pacific Willow
Salix lasiolepsis - Arroyo Willow

Salix lucida - Shining Willow
Salix magnifica
Salix matsudana - Chinese Willow
Salix miyabeana
Salix mucronata
Salix myrtilloides - Swamp Willow
Salix myrsinifolia - Dark-leaved Willow
Salix myrsinites - Whortle-leaved Willow
Salix nakamurana
Salix nigra - Black Willow
Salix pedicellaris - Bog Willow
Salix pentandra - Bay Willow
Salix petiolaris - Slender Willow
Salix phylicifolia - Tea-leaved Willow
Salix planifolia- Planeleaf Willow
Salix polaris - Polar Willow
Salix pseudo-argentea
Salix purpurea - Purple Willow
Salix pyrifolia - Balsam Willow
Salix reinii
Salix repens - Creeping Willow
Salix reticulata - Net-leaved Willow
Salix retusa
Salix rorida
Salix rosmarinifolia - Rosemary-leaved Willow
Salix rupifraga
Salix salicicola
Salix schwerinii
Salix scouleriana - Scouler's Willow
Salix sericea - Silky Willow
Salix serissaefolia
Salix serissima - Autumn Willow
Salix shiraii
Salix sieboldiana
Salix sitchensis
Salix subfragilis
Salix subopposita
Salix taraikensis
Salix tetrasperma
Salix thorelii
Salix triandra - Almond Willow
Salix udensis
Salix viminalis - Common Osier
Salix vulpina
Salix waldsteiniana

Salix wallichiana
Salix yezoalpina
Salix yoshinoi

The *willows* are deciduous trees and shrubs in the genus *Salix*, part of the willow family Salicaceae.

There are about 350 species in this genus worldwide, found primarily on moist soils in cooler zones in the Northern Hemisphere. The leaves are deciduous, often elongate but round to oval in a few species, and with a serrated margin. Willows are dioecious with male and female flowers appearing as catkins on different plants; the catkins are produced early in the spring, often before the leaves or as the new leaves open. The fruit is a small capsule containing numerous tiny (0.1 mm) seeds embedded in white down, which assists wind dispersal of the seeds. Willows are very cross-fertile and numerous hybrids are known, both naturally occurring and in cultivation.

Some smaller species may also be known by the common names osier and sallow; the latter name is derived from the same root as the Latin salix.

Some willows, particularly arctic and alpine species, are very small; the *Dwarf Willow* (Salix herbacea) rarely exceeds 6 cm in height, though spreading widely across the ground.

The *Weeping Willow*, very widely planted as an ornamental tree, is a cultivar, Salix × sepulcralis 'Chrysocoma', derived from a hybrid between the Chinese Peking Willow and the European White Willow.

Almost all willows take root very readily from cuttings or where broken branches lie on the ground. There are a few exceptions, including the Goat Willow and Peachleaf Willow. One famous example of such growth from cuttings involves the poet Alexander Pope, who begged a twig from a parcel tied with twigs sent from Spain to Lady Suffolk. This twig was planted and thrived, and legend has it that all of England's Weeping Willows are descended from this first one [1]. Willows are used as food plants by the larvae of some Lepidoptera species - see list of Lepidoptera which feed on Willows.

Uses

Medicinal uses

The bark of the willow tree has been mentioned in ancient texts from Assyria, Sumer and Egypt as a remedy for aches and fever, and the Greek physician Hippocrates wrote about its medicinal properties in the 5th century BC. Native Americans across the American continent relied on it as a staple of their medical treatments.

The active extract of the bark, called salicin, was isolated to its crystalline form in 1828 by Henri Leroux, a French pharmacist, and Raffaele Piria, an Italian chemist, who then succeeded in separating out the acid in its pure state. Salicin is acidic when in a saturated solution in water (pH = 2.4), and is called salicylic acid for that reason.

In 1897 Felix Hoffmann created a synthetically altered version of salicin (in his case derived from the Spiraea plant), which caused less digestive upset than pure salicylic acid. The new drug, formally Acetylsalicylic acid, was named aspirin by Hoffmann's employer Bayer AG. This gave rise to the hugely important class of drugs known as non-steroidal anti-inflammatory drugs (NSAIDs).

Other uses

- Agroforestry
Basket weaving
Biofiltration
Biomass energy (bioenergy)
Box, Veneer
Charcoal
Constructed wetlands
Cricket bats
Cradle boards
Chairs & furniture
Dolls, toys, whistles
Ecological wastewater treatment systems
Energy forestry
As part of the four species used on the Jewish holiday of Sukkot.
Fibre plants
- Fish traps
- Flutes
Hedges
Land reclamation
Landscaping
Living Willow Sculpture
Paper
Phytoremediation
Poles, turnery, tool handles
Rope and string
Streambank stabilisation (bioengineering)
Slope stabilisation
Soil erosion control
Soil building
Soil reclamation
Shelterbelt & windbreak
Sweat lodges

- Tannin

- Wands, brooms
Wattle fences
Wattle and daub
Wildlife habitat

-

Yeast

Yeasts are single-celled (unicellular) fungi, a few species of which are commonly used to leaven bread, ferment alcoholic beverages, and even drive experimental fuel cells. Most yeasts belong to the division Ascomycota, though some are Basidiomycota. A few yeasts, such as Candida albicans, can cause infection in humans (Candidiasis). More than one thousand species of yeasts have been described. The most commonly used yeast is Saccharomyces cerevisiae, which was domesticated for wine, bread, and beer production thousands of years ago.

Physiology

Yeast species can have either obligately aerobic or facultatively anaerobic physiology. There is no known obligately anaerobic yeast. In the absence of oxygen, fermentative yeasts produce their energy by converting carbohydrates into carbon dioxide and ethanol (alcohol) or lactic acid. In brewing, the ethanol is bottled, while in baking the carbon dioxide raises the bread, and most of the ethanol evaporates.

An example with glucose as the substrate

$C_6H_{12}O_6$ (glucose) ’$2C_2H_5OH + 2CO_2$

Use in biotechnology

The useful physiological properties of yeast have led to their use in the field of biotechnology. Fermentation of sugars by yeast is the oldest and largest application of this technology. Baker's yeast is used for bread production, brewer's yeast is used for beer fermentation, and yeast is also used for wine fermentation. Yeast are also one of the most widely used model organisms for genetics and cell biology.

Growth environment

Many yeasts can be isolated from sugar-rich environmental samples. Some good examples include fruits and berries (such as grapes, apples or peaches), exudates from plants (such as plant saps or cacti). Some yeasts are found in association with soil and insects.

A common medium used for the cultivation of yeasts is called potato dextrose agar (PDA) or potato dextrose broth. Potato extract is made by autoclaving (i.e. pressure-cooking) cut-up potatoes with water for 5 to 10 minutes and then decanting off the broth. Dextrose (glucose) is then added (10 g/L) and the medium is sterilized by autoclaving.

Monoclonal antibodies

Monoclonal antibodies (*mAb*) are antibodies that are identical because they were produced by one type of immune cell and are all clones of a single parent cell. Given (almost) any substance, it is possible to create monoclonal antibodies that specifically bind to that substance; they can then serve to detect or purify that substance. This has become an important tool in biochemistry, molecular biology and medicine. When used as medications, the generic name ends in -mab (see "Nomenclature of monoclonal antibodies").

Discovery

The idea of a "magic bullet" was first proposed by Paul Ehrlich who at the beginning of the 20th century figured that if a compound could be made that selectively targeted a disease-causing organism, then a toxin for that organism could be delivered along with the agent of selectivity.

In the 1970s the B-cell cancer myeloma was known, and it was understood that these cancerous B-cells all produce a single type of antibody (a paraprotein). This was used to study the structure of antibodies, but it was not yet possible to produce identical antibodies specific to a given antigen.

The process of producing monoclonal antibodies described above was invented by Georges Köhler, César Milstein, and Niels Kaj Jerne in 1975[1]; they shared the Nobel Prize in Physiology or Medicine in 1984 for the discovery. The key idea was to use a line of myeloma cells that had lost their ability to secrete antibodies, come up with a technique to fuse these cells with healthy antibody producing B-cells, and be able to select for the successfully fused cells.

In 1988 Greg Winter and his team pioneered the techniques to humanise monoclonal antibodies[2], removing the reactions that many monoclonal antibodies caused in some patients.

Production

If a foreign substance (an antigen) is injected into a vertebrate such as a mouse or a human, some of the immune system's B-cells will turn into plasma cells and start to produce antibodies that recognize that antigen. Each B-cell produces only one kind of antibody, but different B-cells will produce structurally different antibodies that bind to different parts ("epitopes") of the antigen. This natural mixture of antibodies found in serum is known as polyclonal antibodies.

To produce monoclonal antibodies, one removes B-cells from the spleen or lymph nodes of an animal that has been challenged several times with the antigen of interest. These B-cells are then fused with myeloma tumor cells that can grow indefinitely in culture (myeloma is a B-cell cancer) and that have lost the ability to produce antibodies. This fusion is done by making the cell membranes more permeable by the use of polyethylene glycol, electroporation or, of historical importance, infection with some virus. The fused hybrid cells (called *hybridomas*), being cancer cells, will multiply rapidly and indefinitely. Large amounts

of antibodies can therefore be produced. The hybridomas are sufficiently diluted to ensure clonality and grown. The antibodies from the different clones are then tested for their ability to bind to the antigen (for example with a test such as ELISA) or immuno-dot blot, and the most sensitive one is picked out.

In the above process, one uses myeloma cell lines that have lost their ability to produce their own antibodies or antibody chain, so as to not contaminate the target antibody. Furthermore, one employs only myeloma cells that have lost a specific enzyme (hypoxanthine-guanine phosphoribosyltransferase, HGPRT) and therefore cannot grow under certain conditions (namely in the presence of HAT medium). These cells are preselected by the use of 8-azaguanine media prior to the fusion. Cells that possess the HGPRT enzyme will be killed by the 8-azaguanine. During the fusion process many cells can fuse. Myeloma with myeloma, spleen cell with spleen cell, 3 cells of different types etc... The desired fusions are between healthy B-cells producing antibodies against the antigen of interest and myeloma cells. These are relatively rare, but when one succeeds, then the healthy partner supplies the needed enzyme and the fused cell can survive in HAT medium. This is the trick to detect the successfully fused cells. The medium must be enriched during selection to favour hybridoma growth. This can be achieved by the use of a layer of feeder cells or supplement media such as briclone.

Monoclonal antibodies can be produced in cell culture or in live animals. When the hybridoma cells are injected in mice (in the peritoneal cavity, the gut), they produce tumors containing an antibody-rich fluid called ascites fluid. Production in cell culture is usually preferred as the ascites technique may be very painful to the animal and if replacement techniques exist, may be considered unethical. Fermentation chambers have been used to produce antibodies on a larger scale. Nowadays, bioengineering allow production of antibodies in plants.

Applications

Once monoclonal antibodies for a given substance have been produced, they can be used to detect the presence and quantity of this substance, for instance in a Western blot test (to detect a protein on a membrane) or an immunofluorescence test (to detect a substance in a cell). They are also very useful in immunohistochemistry which detect antigen in fixed tissue sections. Monoclonal antibodies can also be used to purify a substance with techniques called immunoprecipitation and affinity chromatography.

Monoclonal antibodies for cancer treatment

One possible treatment for cancer involves monoclonal antibodies that bind only to cancer cell-specific antigens and induce an immunological response against the target cancer cell. Such mAb could also be modified for delivery of a toxin, radioisotope, cytokine or other active conjugate; it is also possible to design bispecific antibodies that can bind with their Fab regions both to target antigen and to a conjugate or effector cell. In fact, every intact antibody can bind to cell receptors or other proteins with its Fc region. The illustration below shows all these possibilities:

Monoclonal antibodies for cancer. ADEPT, antibody directed enzyme prodrug therapy; ADCC, antibody dependent cell-mediated cytotoxicity; CDC, complement dependent cytotoxicity; MAb, monoclonal antibody; scFv, single-chain Fv fragment. [3]

Chimeric and humanized antibodies

One problem in medical applications is that the standard procedure of producing monoclonal antibodies yields mouse antibodies. Although murine antibodies are very similar to human ones there are differences. The human immune system hence recognizes mouse antibodies as foreign, rapidly removing them from circulation and causing systemic inflammatory effects.

A solution to this problem would be to generate human antibodies directly from humans. However, this is not easy primarily because it is clearly not ethical to challenge humans with antigen in order to produce antibody. Furthermore, it is not easy to generate human antibodies against human tissues.

Various approaches using recombinant DNA technology to overcome this problem have been tried since the late 1980s. In one approach, one takes the DNA that encodes the binding portion of monoclonal mouse antibodies and merges it with human antibody producing DNA. One then uses mammalian cell cultures to express this DNA and produce these half-mouse and half-human antibodies. (Bacteria cannot be used for this purpose, since they cannot produce this kind of glycoprotein.) Depending on how big a part of the mouse antibody is used, one talks about *chimeric antibodies* or *humanized antibodies*. Another approach involves mice genetically engineered to produce more human-like antibodies. Monoclonal antibodies have been generated and approved to treat;cancer, cardiovascular disease, inflammatory diseases, macular degeneration, transplant rejection, and viral infection (see monoclonal antibody therapy).

In August 2006 the Pharmaceutical Research and Manufacturers of America reported that U.S. companies had 160 different monoclonal antibodies in clinical trials or awaiting approval by the Food and Drug Administration.[4]

See also

- Monoclonal antibody therapy
- Nomenclature of monoclonal antibodies

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Nomenclature of monoclonal antibodies

The *nomenclature of monoclonal antibodies* is a naming scheme for assigning generic, or nonproprietary, names to a group of medicines called monoclonal antibodies. This scheme is used for both the World Health Organization's International Nonproprietary Names and the United States Adopted Names. In general, suffixes are used to identify a class of medicines; all monoclonal antibody pharmaceuticals end with the suffix -mab. However, different infixes are used depending on the structure and function of the medicine.

The infix preceding the -mab suffix denotes the animal origin of the antibodies. Although the original monoclonal antibodies were produced in mice (infix, -o-), these antibodies are recognized as foreign by human immune systems and may be rapidly cleared, provoke an allergic reaction, or both. Therefore, parts of the antibody may be replaced with human sequences. If the constant region is replaced with the human form, it is termed chimeric and the infix used is -xi-. Part of the variable regions may also be substituted, in which case it is termed humanized and the infix used is -zu-. Antibodies originating in humans use -u-.

The infix preceding the source of the antibodies refers to medicine's target. Most of these consist of a consonant, vowel, then another consonant. For ease of pronunciation and to avoid awkwardness, the final consonant is dropped if the following infix begins with a consonant (such as -zu- or -xi-). Examples of these include -ci(r)- for the circulatory system and -tu(m)- for miscellaneous tumors (cancers).

Finally, the prefix carries no special meaning and should be unique for each medicine. A second word may be added if there is another substance attached or linked.

Complete list of stems for monoclonal antibody nomenclature

Prefix	Target		Source		Suffix
varies	*-vi(r)-*	viral	*-u-*	human	*-mab*
	-ba(c)-	bacterial	*-o-*	mouse	
	-li(m)-	immune	*-a-*	rat	
	-le(s)-	infectious lesions	*-e-*	hamster	
	-ci(r)-	cardiovascular	*-i-*	primate	
	-co(l)-	colonic tumor	*-xi-*	chimeric	
	-me(l)-	melanoma	*-zu-*	humanized	
	-ma(r)-	mammary tumor			
	-go(t)-	testicular tumor			
	-go(v)-	ovarian tumor			
	-pr(o)-	prostate tumor			
	-tu(m)-	miscellaneous tumor			

Examples

Abciximab is a commonly used medication to prevent platelets from clumping together. It can be broken down into *ab- + -ci(r)- + -xi- + -mab*. Therefore, it is a chimeric monoclonal antibody used on the cardiovascular system.

Another example is the breast cancer medication trastuzumab, which can be broken down into *tras- + -tu(m)- + -zu- + -mab*. Therefore, it is a humanized monoclonal antibody used against a tumor.

Muscle relaxant

A *muscle relaxant* is a drug which decreases the tone of a muscle.

Central acting muscle relaxants

- Benzodiazepines
  - Methocarbamol

Unclassified

Here are several other skeletal muscle relaxants which may belong in the above categories:

- Baclofen
Carisoprodol
Chlorzoxazone
Cyclobenzaprine
Dantrolene
Metaxalone
Orphenadrine
Pancuronium
Tizanidine

Acting on smooth muscle

- Dicyclomine

Other

Drugs from classes other than the muscle relaxant class are also used to treat spasticity:

- Clonidine
Gabapentin

Neuromuscular-blocking drugs

Neuromuscular-blocking drugs block neuromuscular transmission at the neuromuscular junction, causing paralysis of the affected skeletal muscles. This is accomplished either by acting presynaptically via the inhibition of acetylcholine (ACh) synthesis or release, or by acting postsynaptically at the acetylcholine receptor. While there are drugs that act presynaptically (such as botulin toxin and tetrodotoxin), the clinically-relevant drugs work postsynaptically.

Clinically, neuromuscular block is used as an adjunct to anesthesia to induce paralysis, so that surgery can be carried out with less complications. Because neuromuscular block may paralyze muscles required for breathing, mechanical ventilation should be available to maintain adequate respiration. These drugs fall into two groups:

- *Non-depolarizing blocking agents*: These agents constitute the majority of the clinically-relevant neuromuscular blockers. They act by blocking the binding of ACh to its receptors, and in some cases, they also directly block the ionotropic activity of the ACh receptors (PMID 8866353).
- *Depolarizing blocking agents*: These agents act by depolarizing the plasma membrane of the skeletal muscle fiber. This persistent depolarization makes the muscle fiber resistant to further stimulation by ACh.

Patients are still aware of pain even after full conduction block has occurred; hence, general anesthetics and/or analgesics must be given to prevent anesthesia awareness.

Non-depolarizing blocking agents

All of these agents act as competitive antagonists against ACh at the site of postsynaptic ACh receptors.

Tubocurarine, found in curare of the South American plant genus Strychnos, has this effect. Tubocurarine has a slow onset (>5min) and a long duration of action (1-2 hours). Side effects include hypotension. This hypotension is partially explained by its effect of increasing histamine release, which is a vasodilator (PMID 2429800), as well as its effect of blocking autonomic ganglia (PMID 2682131). Route of excretion in the urine.

This drug needs to block about 70-80% of the Ach receptors for neuromuscular conduction to fail, and hence, for effective blockade to occur. At this stage, EPPs (end-plate potentials) can still be detected, but are too small the reach the threshold potential needed for activation of muscle fiber contraction.

Depolarizing blocking agents

Depolarizing blocking agents work by depolarizing the plasma membrane of the muscle fiber, similar to acetylcholine. However, these agents are resistant to degradation by acetylcholinesterase, and can persistently depolarize the muscle fibers as opposed to the transient depolarization by ACh which is rapidly degraded. Initially, they cause muscular fasciculations (muscle twitches) while they are depolarizing the muscle fibers. Eventually, after sufficient depolarization has occurred, the muscle is no longer responsive to ACh released by the motoneurons. Hence, full neuromuscular block has been achieved.

Decamethonium and suxamethonium (US: succinylcholine) are good examples of this. These drugs are ACh-like drugs, which have short action time, and elevated action effects at the end-plate of muscles. Suxamethonium is the only depolarizing blocking agent in general clinical use.

Inhibition of acetylcholinesterase, the enzyme responsible for degrading acetylcholine, will cause ACh to have the same effect as these agents.

Comparison of drugs

The main difference is in the reversal of these two types of neuromuscular-blocking drugs. Non-depolarizing blockers are reversed by anticholinesterase inhibitor drugs. Since they are competitive antagonists at the ACh receptor so can be reversed by increases in ACh. The depolarizing blockers already have ACh-like actions, so these agents will have prolonged effect under the influence of anticholinesterase inhibitors.

The administration of depolarizing blockers will initially exhibit fasciculations (a sudden twitch just before paralysis occurs). This is due to the depolarization of the muscle. Also, post-operative pain is associated with depolarizing blockers.

The tetanic fade is the failure of muscles to maintain a fused tetany at sufficiently-high frequencies of electrical stimulation. Non-depolarizing blockers will have this effect on patients, while depolarizing blockers will not.

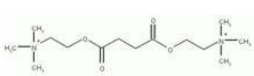
Adverse effects

Since these drugs may cause paralysis of the diaphragm, mechanical ventilation should be at hand to provide respiration.

Additionally, these drugs may exhibit cardiovascular effects, since they are not fully selective for the nicotinic receptor and hence may have effects on muscarinic receptors (PMID 2682131). If muscarinic receptors of the autonomic ganglia or adrenal medulla are blocked, these drugs may cause hypotension and tachycardia. Additionally, neuromuscular blockers may facilitate histamine release, which causes hypotension, flushing, and tachycardia.

In depolarizing the musculature, suxamethonium may trigger the release of large amounts of potassium from muscle fibers. This puts the patient at risk for life-threatening complications, such as hypokalemia and cardiac arrhythmias.

Suxamethonium chloride



Systematic (IUPAC) name

2,2'-[(1,4-dioxobutane-1,4-diyl)bis(oxy)]bis (N,N,N-trimethylethanaminium)

Identifiers

CAS number 306-40-1

ATC code M03**AB01**

PubChem 5314

DrugBank APRD00159

Chemical data

Formula $C_{14}H_{30}N_2O_4$

Mol. weight 290.399 g/mol

Pharmacokinetic data

Bioavailability **NA**

Metabolism By pseudocholinesterase, to succinylmonocholine and choline

Excretion Renal (10%)

Therapeutic considerations

Pregnancy cat. A(AU) C(US)

Legal status POM(UK) -only(US)

Routes Intravenous

Suxamethonium chloride (also known as *succinylcholine*, or *scoline*) is a white crystalline substance, it is odourless and highly soluble in water. The compound consists of two acetylcholine molecules that are linked by their acetyl groups. Suxamethonium is sold under several trademark names such as *Anectine*®, and may be referred to as "sux" for short.

Suxamethonium acts as a depolarizing muscle relaxant. It imitates the action of acetylcholine at the neuromuscular junction, but it is not degraded by acetylcholinesterase but by pseudocholinesterase, a plasma cholinesterase. This hydrolysis by pseudocholinesterase is much slower than that of acetylcholine by acetylcholinesterase.

Phase 1 block

There are two phases to the blocking effect of suxamethonium. The first is due to the prolonged stimulation of the acetylcholine receptor results first in disorganized muscle contractions (fasciculations, considered to be a side effect as mentioned below), as the acetylcholine receptors are stimulated. On stimulation, the acetylcholine receptor becomes a general ion channel, so there is a high flux of potassium out of the cell, and of sodium into the cell, resulting in a membrane potential less than the action potential. So, after the initial firing, the cell remains refractory.

Phase 2 block

On continued stimulation, the acetylcholine receptors become desensitised and close. This means that new acetylcholine signals do not cause an action potential; and the continued binding of suxamethonium is ignored. This is the principal anaesthetic effect of suxamethonium, and wears off as the suxamethonium is degraded, and the acetylcholine receptors return to their normal configuration. The side effect of hyperkalaemia is because the acetylcholine receptor is propped open, allowing continued flow of potassium ions into the extracellular fluid. A typical increase of potassium ion serum concentration on administration of suxamethonium is 0.5 mmol per litre, whereas the normal range of potassium is 3.5 to 5 mmol per litre: a significant increase which results in the other side-effects of ventricular fibrilation due to reduced to action potential initiation in the heart.

Medical uses

Its medical uses are limited to short-term muscle relaxation in anesthesia and intensive care, usually for facilitation of endotracheal intubation. Despite its many undesired effects on the circulatory system and skeletal muscles (including malignant hyperthermia, a rare but life-threatening disease), it is perennially popular in emergency medicine because it arguably has the fastest onset and shortest duration of action of all muscle relaxants. Both are major points of consideration in the context of trauma care, where paralysis must be induced very quickly and the use of a longer-acting agent might mask the presence of a neurological deficit.

A single intravenous dose of 1.0 to 1.5 milligrams per kilogram of body weight for adults or 2.0 milligrams per kilogram for pediatrics will cause flaccid paralysis within a minute of injection. For intramuscular injection higher doses are used and the effects last somewhat longer. Suxamethonium is quickly degraded by plasma cholinesterase and the duration of effect is usually in the range of a few minutes. When plasma levels of cholinesterase are greatly diminished or an atypical form of cholinesterase is present (an otherwise harmless inherited disorder), paralysis may last much longer.

Side effects

Side effects include fasciculations, muscle pains, acute rhabdomyolysis with hyperkalemia, transient ocular hypertension, and changes in cardiac rhythm including bradycardia, cardiac arrest, and ventricular dysrhythmias. In children with unrecognized neuromuscular diseases, a single injection of succinylcholine can lead to massive release of potassium from skeletal muscles with cardiac arrest.

Succinylcholine does not produce unconsciousness or anesthesia, and its effects may cause considerable psychological distress while simultaneously making it impossible for a patient to communicate. For these reasons, administration of the drug to a conscious patient is strongly contraindicated, except in necessary emergency situations.

This drug has occasionally been used as a paralyzing agent for executions by lethal injection, although pancuronium bromide is the preferred agent today because of its longer duration of effect and its absence of fasciculations as a side effect. It has also been used for murder.

Succinylcholine is the drug that is suspected to have been used to murder Nevada State Controller Kathy Augustine.

Nootropic

Nootropics, popularly referred to as "smart drugs," are substances which boost human cognitive abilities (the functions and capacities of the brain). The word *nootropic* is derived from the Greek words noos or mind and tropein meaning to ward. Typically, nootropics are alleged to work by increasing the brain's supply of neurochemicals (neurotransmitters, enzymes, and hormones), by improving the brain's oxygen supply, or by stimulating nerve growth.

Most alleged nootropic substances are nutrients or plant components (herbs, roots, beans, bark, etc.), available over the counter at health food and grocery stores, and are used as nutritional supplements. Some nootropics are drugs, used to treat retardation, neural degradation (Alzheimer's and Parkinson's), and for cases of oxygen deficit to prevent hypoxia. These drugs have a variety of human enhancement applications as well, are marketed heavily on the World Wide Web, and are used by many people in personal cognitive enhancement regimens.

With some nootropics the effects are subtle and gradual, such as with most nerve growth inducers, and may take weeks or even months before any cognitive improvement is noticed. At the other end of the spectrum are nootropics which have effects that are immediate, profound, and obvious. While scientific studies support some of the claimed benefits it is alleged that certain nootropic substances provide, It is worth noting that many of the claims attributed to a variety of nootropics have not been formally tested. Citations are provided in the article where information is available.

General strategies

Neurotransmitter support - supplying the body with the precursors and cofactors it needs to produce neurotransmitters. Keeping the brain's neurotransmitters at high levels improves concentration, mental focus, calculation ability, memory encoding, recall, creativity, mood, and cures and prevents most depressions. The four main neurotransmitters are acetylcholine, dopamine, norepinephrine and serotonin.

Note that cardiovascular exercise performed on a regular basis also has nootropic effects, by increasing the body's capacity to supply brain cells with oxygen. Exercise is highly synergistic with nutritional supplementation, and a health regimen is incomplete without it.

Nootropic substances

Nootropic drugs are generally only available by prescription or through personal importation. The other nootropic substances listed below are either nutritional supplements or plant components, and are generally available over the counter at health food and grocery stores. The term "drug" here is used as a legal designation, and does not indicate greater efficacy. With nootropics, the effects, effectiveness, and potency differ from substance to substance and from individual to individual. See the substance descriptions below for more detail.

Replenishing and increasing neurotransmitters

Thinking is a biologically demanding task. It involves the firing of neurons which requires plenty of neurotransmitters, and even though these are reuseable to some extent, they do get depleted. Depletion of neurotransmitters generally results in reduced mental performance, which may include difficulty concentrating, slowed reasoning, decreased learning efficiency, impaired recall, reduced coordination, lowered moods, inability to cope, increased response times, and mental fatigue. This also generally increases the likelihood of human error on tasks and activities performed. Stress causes neurotransmitters to be depleted even faster. The brain's neurotransmitters need to be replenished frequently, made by the body from substances ingested in the diet. Maintaining neurochemicals at optimal levels has a corresponding effect on brain performance, supporting improved mental agility and stamina, even beyond the individual's normal limits.

As the brain ages, its ability to produce and maintain youthful levels of neurotransmitters declines.[1] Thus, the theory is that by providing the brain with ample raw materials to make the neurotransmitters it needs can restore them to more youthful levels to help maintain cognitive function at vigorous youthful levels as well.

Cholinergics

Cholinergics are substances which affect the neurotransmitter acetylcholine or the components of the nervous system which utilize acetylcholine. Acetylcholine facilitates memory, concentration, focus, and high-order thought processes (abstract thought, calculation, innovation, etc.). Increasing the availability of this neurotransmitter in the brain may improve these functions and increase the duration in which they may be engaged without slowing down or stopping. Oversupplying the brain with acetylcholine may have the opposite effect, temporarily reducing rather than improving mental performance. Cholinergic nootropics include acetylcholine precursors and cofactors, and acetylcholinesterase inhibitors:

- Acetyl-L-carnitine (ALCAR) - Amino acid. Precursor of acetylcholine (donating the acetyl portion to the acetylcholine molecule). It is synergistic with lipoic acid.
- Centrophenoxine (Lucidril) - Drug. cholinergic agent, enhances color perception.
- Choline - precursor to acetylcholine (an essential component of the acetylcholine molecule).
    - Alpha-GPC (L-alpha glycerylphosphorylcholine, Choline alfoscerate) - most effective choline precursor, readily crosses the blood-brain barrier.
    - CDP-Choline (Cytidine Diphosphate Choline) - choline precursor, tends to be less expensive and similar in effect to Alpha GPC.
    - Choline bitartrate - precursor of acetylcholine, general nootropic, anti-depressant.
    - Choline citrate - precursor of the neurotransmitter acetylcholine, general nootropic, anti-depressant.

- DMAE - approved treatment for ADD/ADHD, precursor of acetylcholine, cholinergic agent, removes lipofuscin from the brain, anti-depressant.
- L-Huperzine A - potent acetylcholinesterase inhibitor derived from Chinese club-moss.
- Lecithin - precursor of acetylcholine.
- Pyrrolidone derivatives:
  - Piracetam (Nootropil) - Prescription drug (in Europe). The original (first)[2], and most commonly taken[3] nootropic drug. It is a cholinergic agent, synergistic with DMAE, centrophenoxine, choline, and Hydergine. Increases brain cell metabolism and energy levels[4], and speeds up interhemispheric flow of information (left-right brain hemisphere communication). Increases vigilance,[5], improves concentration, and enhances memory. Protects neurons from hypoxia,[2] and stimulates growth of acetylcholine receptors. May also cause nerves to regenerate. Piracetam markedly decreases the formation of neuronal lipofuscin.[6] It improves posture in elderly people.[7] It is not regulated in the US.
  - Aniracetam - Drug. Analog of piracetam, and 4 to 8 times more potent. Like piracetam, aniracetam protects against some memory impairing chemicals, such as diethyldithiocarbamate and clonidine.[8] Also like piracetam, aniracetam may enhance memory in aging adults by increasing levels of brain biogenic monoamines, which are beneficial to learning and memory.[1] Both racetams have possible therapeutic use in treating fetal alcohol syndrome.[9] Aniracetam increases vigilance.[5]
  - Etiracetam - It increases vigilance.[5]
  - Nefiracetam - Drug. Analog of piracetam, and facilitates hippocampal neurotransmission.[10]
  - Oxiracetam - Drug. Analog of piracetam, and 2 to 4 times stronger. Improves memory, concentration, and vigilance. When fed to pregnant rats, the offspring of those rats were more intelligent than the offspring of rats fed a saline solution placebo.
  - Pramiracetam - Drug. Fifteen times stronger than piracetam, of which it is an analog.
- Vitamin B5 - cofactor in the conversion of choline into the neurotransmitter acetylcholine, cholinergic agent, increases stamina (including mental stamina).

CAUTION: Excess acetylcholine can be potentially harmful; see cholinesterase inhibitor.

Dopaminergics

Dopaminergics are substances which affect the neurotransmitter dopamine or the components of the nervous system which utilize dopamine. Dopamine is produced in the synthesis of all catecholamine neurotransmitters, and is the rate limiting step for this

synthesis. Dopaminergic nootropics include dopamine precursors and cofactors, and dopamine reuptake inhibitors:

- L-dopa - Prescription drug. Precursor to the neurotransmitter dopamine, general nootropic, anti-depressant.
- Phenylalanine (requires Vitamin B6 and Vitamin C) - Essential amino acid. Precursor to dopamine, general nootropic, anti-depressant, sleep reducer.
- Theanine - Found in tea. Increases serotonin and dopamine levels in the brain. Increases alpha-wave based alert relaxation.
- Tyrosine (requires Vitamin B6 and Vitamin C) - Amino acid. Precursor to dopamine, general nootropic, anti-depressant, sleep reducer.
- Vitamin C- improves cardiovascular elasticity and integrity, membrane stabilizer and major anti-oxidant (protects brain cells and prevents brain cell death), cofactor in the production of the neurotransmitters dopamine and serotonin.
- Vitamin B6 - co-factor used by the body to produce dopamine.
- Yohimbe - Bark. Boosts dopamine levels as much as 80%, though how it does this is not yet understood. Aphrodesiac. Yohimbe poses some health risks through its side-effects: it is a neuro-paralytic which slows down breathing and induces acidosis, some symptoms of which are malaise, nausea, and vomiting. Contraindicated for users of megadoses of acidic vitamins or nutrients.

Deprenyl - Blocks MAO B (the neuroenzyme that breaks down dopamine) thus raising Dopamine better and faster than other drugs.

Serotonergics

Serotonergics are substances which affect the neurotransmitter serotonin or the components of the nervous system which utilize serotonin. Serotonergic nootropics include serotonin precursors and cofactors, and serotonin reuptake inhibitors:

- 5-HTP - more bioavailable form of tryptophan, precursor to the neurotransmitter serotonin, promotes relaxed poise and sound sleep.
- Griffonia simplicifolia a natural source of 5-HTP (an alternative in countries where 5-HTP not legal, freely available.)
- Theanine - Found in tea. Increases GABA and dopamine levels in the brain. Increases alpha-wave based alert relaxation.
- Tryptophan (requires Vitamin B6 and Vitamin C) - Essential amino acid. Precursor to serotonin, found in high concentration in bananas and poultry (especially turkey), also in milk, promotes relaxed poise and sound sleep.

Anti-depression, adaptogenic and mood stabilization

Depression and depressed mood negatively affect cognitive performance. Feelings of sadness, guilt, helplessness, hopelessness, anxiety, and fear caused by depression detract from productive thought, while apathy (which is also induced by depression) is the lack of

motivation and driving moods (like curiosity, interest, determination, etc.) Other symptoms include disturbed sleep patterns, mental fatigue and loss of energy, trouble concentrating or making decisions, and a generalized slowing and obtunding of cognition, including memory. Obviously, removing these effects improves intelligence and mental performance, and therefore, counteracting and preventing depression are effective nootropic strategies. There is a high correlation between depression and a reduction or depletion of neurotransmitters (dopamine, acetylcholine, and serotonin) in the brain, therefore it is no surprise that increasing the brain's supply of neurotransmitters alleviates (or at least reduces the symptoms of) most depressions. Stress is another major factor in neurotransmitter depletion, being both a cause and effect of it (creating a vicious downward cycle), therefore stress management and anti-stress substances are also very useful nootropic strategies.

All of the "nergics" listed above have been found to increase stress tolerance and alleviate depression (by replenishing or increasing the brain's supply of specific neurotransmitters), especially when used in precursor/co-factor combinations.

Here are some more nootropics which affect mood and stress:

- Ashwagandha (Withania somnifera) - Root. Also known as Indian ginseng. Adaptogen used as a tonic to normalize body processes and reduce stress and anxiety.
- Inositol - Is a B-vitamin like substance with anti-anxiety effects. It is believed to produce its anti-anxiety effects by improving the binding of gabaergics to GABA***A*** receptors. Inositol is a sugar, and is therefore an alternative energy source for brain and muscle tissues. It produces a sugar high without a sugar low, making it especially suited for sweetening tea (instead of sugar). It is also a membrane stabilizer which can strengthen (and therefore help protect) neurons.
- Lemon Balm (Melissa Officinalis) - Herb. Anti-depressant.
- Rhodiola Rosea - Herb. Adaptogen; elevates mood, alleviates depression. Promotes mental energy and stamina, reduces fatigue.
- St John's Wort - Herb. The active components: hypericin and hyperforin, are clinically indicated to be effective in cases of mild to medium depression.
- Ginseng, Siberian (Eleutherococcus senticosus) - Root. Anti-anxiety adaptogen that normalizes physical stress and mental consequences.
- Selegiline (Deprenyl) - Along with Piracetam and Meclofenoxate, Deprenyl decreases the amount of lipofuscin pigment and ceroid pigment accumulations in the brain by improving cellular recycling activities.[11] Therefore, these nootropics may slow age related diseases in the brain.
- Sutherlandia Frutescens - Herb. Adaptogen, blood detoxifier.
- Tea - Herb. Contains theophylline and theanine. Increases alpha-wave based alert relaxation (relieves stress).
- Theanine - Amino acid. Found in tea. Increases serotonin and dopamine levels in the brain. Increases alpha-wave based alert relaxation.
- Vasopressin - Drug. Memory hormone produced by the pituitary gland which improves both memory encoding and recall. Rapidly counters chronic apathy syndrome and drug-induced vasopressin depletion.

- Nicotinic acid (vitamin B3) - Essential nutrient. Mild enhancer of concentration and memory. Vasodilator. Mood stabilizer, with a powerful anti-anxiety effect — perhaps the best and most immediate stress reliever available (note that other forms of vitamin B3 do not have this effect). Side effects: gastric upset (which is easily prevented and relieved with antacids), reduced blood pressure and flushing of the skin (caused by vasodilation), and itchy sensation in the skin caused by histamine release.

Brain energy and improved oxygen supply

- Acetyl-L-carnitine (ALCAR) - Amino acid. Transports fatty acids through cellular membranes and cytosol into cells' mitochondria, where the fats undergo oxidation to produce ATP, the universal energy molecule. Synergistic with lipoic acid.
- Chromium- stabilises blood sugar levels promoting concentration.
- Coenzyme q-10 syn. Ubiquinone - increases oxygen transport through the mitochondria of the cells. Appears to slow age-related dementia.
- Creatine - increases brain energy levels via ATP production.
- Inositol -
- Lipoic acid - synergistic with Acetyl-L-carnitine.
- Pyritinol (Enerbol) - Drug. Enhances oxygen and glucose uptake in the brain, and allows glucose to pass more easily through the blood-brain barrier. Improves general brain function. It is also a powerful anti-oxidant which scavenges hydroxyl radicals created in the very processes it is involved in.
- Vinpocetine - micro-circulation enhancer, improves oxygen supply to brain cells.

Mental agility, concentration, stamina, and focus

- Adrafinil (Olmifon) - Drug.
- Caffeine - improves concentration, idea production, but hinders memory encoding. Also produces the jitters. Caffeine is the most widely used psychoactive substance in the world.
- Coffee - Bean. Contains caffeine; brewed coffee is high in antioxidants.
- Nicergoline - Drug. Nicergoline is an ergoloid mesylate derivative used to treat senile dementia. It has also been found to increase mental agility and enhance clarity and perception. It increases vigilance.[5] Increases arterial flow and use of oxygen and glucose in the brain.
- Nicotine - stimulus barrier (aids in concentration). Stimulus barrier rebound effect (an unpleasant side effect).
- Cocaine - Drug
    - Methylphenidate (Ritalin) - Drug
- Phenibut -

- Theophylline **-**

Memory enhancement and learning improvement

All of the "nergics" listed above improve memory (encoding and recall). So do all nootropics which improve general brain performance such as the brain energy and oxygen suppliers listed above, and the nerve growth stimulants and protectants listed in their own section below. Other nootropics with specific effects on memory encoding and recall include:

- Bacopa monniera Linn. (Brahmi) - Herb. Elevates curiosity, enhances memory and concentration.[12] Brahmi also protects against amnesia inducing chemicals such as scopolamine or loss of memory due to electro convulsive shocks.[12] It is a traditional ayurvedic medicine.
- Rosemary - Herb. Rosemary has a very old, albeit unverified reputation for improving memory.

- **Vasopressin -** Hormone**,** prescription drug**.**

Nerve growth stimulation and brain cell protection

- Acetyl-L-carnitine (ALCAR) - Amino acid. Inhibits lipofuscin formation.
- Bacopa monnieri (Brahmi) - Herb. Improves protein synthesis in brain cell repair and new dendritic growth.
- Selegiline (Deprenyl) - Drug. Brain cell protectant, delays senescence of brain cells, proven to increase maximum life span in laboratory rats.
- Ergoloid mesylates (Hydergine) - Drug. Mimics nerve growth factor (NGF), and is a powerful anti-oxidant capable of delaying brain death in cases of heart failure and stroke by several minutes with regular use. It increases vigilance.[5]
- Idebenone - stimulates nerve growth, and has same effects as Coenzyme q-10 without its harmful side-effects.
- Inositol - Membrane stabilizer. Strengthens neurons, making them less susceptible to damage.
- Pyritinol (Enerbol) - Drug. Powerful anti-oxidant which scavenges hydroxyl radicals. Also enhances oxygen and glucose uptake in the brain, and allows glucose to pass more easily through the blood-brain barrier. Improves general brain function.
- Rasagiline (Azilect) - Drug. Treats Parkinson's disease either as monotherapy (by itself) or in addition to levodopa therapy. Promotes increased and sustained levels of dopamine by selectively inhibiting an enzyme, monoamine oxidase-B.
- Vitamin C - Membrane stabilizer, involved in collagen synthesis. Strengthens neurons, making them less susceptible to damage. Vitamin C is also a co-factor in the brain's production of dopamine, and therefore it also has general nootropic effects.

Sleep enhancement or reduction

- Vitamin B12 - Can greatly enhance the color of dreams. Stimulates brain neuron RNA synthesis.

Recreational drugs with purported nootropic effects

- Amphetamine (Adderall, Dexedrine) - Schedule II / Class B drugs. Prescribed for attention-deficit disorders, narcolepsy, and certain cases of obesity; and issued as an anti-fatigue pill for pilots in the armed forces. These also heighten alertness, mental focus, vigilance, stamina, and sex drive. They are highly addictive, and have many side effects. Personal importation is prohibitted. Using these recreationally or for performance enhancement is illegal in most countries.
- LSD - Schedule I / Class A drug. At minuscule doses (1 mcg) the drug has effects similar to Hydergine. Overdose and side-effects: produces inebriating hallucinogenic and entheogenic effects at doses as low as 20–30 ¼g (micrograms), with the likelihood of having a bad trip increasing as dose is increased if these effects are undesired. May also cause cognitive shifts, synesthesia, and flashbacks. The drug sometimes spurs long-term or even permanent changes in a user's personality and life perspective.
- 4-methylaminorex
- Pemoline

- Psilocybin

- Psilocin

Other nootropics

- Adafenoxate - Has an anti-anxiety effect for rats[13] and possibly the same for humans.

Butea frondosa - "The plant Butea frondosa has been indicated in the Indian system of medicine as a plant augmenting memory and as a rejuvenator. ... B. frondosa possesses antistress and weak nootropic activity."[14]

BMY 21502 - Injured animals treated with BMY-21502 at one week post-injury showed significant improvement in post-injury learning ability compared to injured animals treated with vehicle. Paradoxically, in uninjured control animals BMY-21502 treatment appeared to worsen learning scores. The results of this study indicate that BMY-21502 may be useful for attenuating the dysfunction in learning ability that occurs following TBI.

Cabergoline (Dostinex) -

Celastrus Panicaltus - Herb.

Cerebrolysin - A neuroprotective nootropic agent, might affect Alzheimer's disease pathology. Currently in clinical trials

Coluracetam - It may also have potential use in prevention and treatment of ischemic retinopathy and retinal and optic nerve injury.

Desmopressin (DDAVP) - Drug. Analog of vasopressin (the anti-diuretic and memory hormone)

DHEA -
Dostinex -
Fasoracetam -
Essential Fatty Acids- EPA (eicosapentaenoic acid) and DHA (docosahexaenoic acid) are the best known. EPA in particular, has an anti-depressant function and is positively indicated in trials with autism and learning difficulties.
Fipexide (Vigilor) - It protects against some memory impairing chemicals, such as diethyldithiocarbamate and clonidine.[8]
Gabapentin (Neurontin) - Anticonvulsant with nootropic effects
Galantamine - Drug.
Gerovital H3 -
Ginkgo biloba - Root. Increases blood flow to the extremities including the brain, nootropic effects are disputed.
Gotu Kola - Herb and root.
Meclofenoxate - Has an anti-anxiety effect for rats[13] and possibly the same for humans. Like Fipexide, it protects against some memory impairing chemicals, such as diethyldithiocarbamate and clonidine.[8] Like many racetams, it may treat fetal alcohol syndrome.[9]
Milacemide - Drug.
Nimodipine -
Ondansetron -
Oxiracetam (Neuromet) -
Phenytoin (Dilantin) -
Phosphatidylserine- reduces age-related memory loss and promotes concentration.
Picamilon - Drug.
Pikamilone -
Pregnenolone -
Propranolol (Inderal) - Drug. Flight response inhibitor, treats phobias, anti-anxiety effect. Though it has a host of negative side effects including but not limited to diabetes complications, depression, and impotence.
Pyroglutamate -
Semax - A neuropeptide (stimulator of the nervous system) developed from a short fragment of ACTH, Pro8-Gly9-Pro10 ACTH(4-10). Claims of significant increase in salvation of neurons are made
Somatotropin -
Sulbutiamine (Arcalion) - Drug.
Xanthinol -

Related pages

Health

- Drug

- Parasympathomimetics
- Prescription drug
    - Psychoactive drug (aka psychotropic drug)
- Psychedelic drug

- Neurodegenerative disease
    - Parkinson's disease

Notes

1. ^ a b Stancheva et al. 1991
2. ^ a b McDaniel et al. 2002
3. ^ Goldman et al., 1999 cited in McDaniel et al. 2002
4. ^ Gabryel & Trzeciak 1994 cited in McDaniel et al. 2002
5. ^ a b c d e Saletu & Grunberger 1985
6. ^ Paula-Barbosa et al. 1991
7. ^ Riedel et al.
8. ^ a b c Genkova-Papasova & Lazarova-Bakurova 1988
9. ^ a b Vaglenova & Petkov 2001
10. ^ Nomura & Nishizaki 2000
11. ^ Riga & Riga 1995
12. ^ a b Singh & Dhawan 1997
13. ^ a b Petkov et al. 1987
14. ^ Soman et al. 2004

Books

- The Edge Effect. Reverse or prevent Alzheimer's, aging, memory loss, weight gain, sexual dysfunction and more. By Eric R Braverman MD. Excellent book describing the four primary neurotransmitters, the role they play in mental and physical functioning, and how to increase levels in the brain. ISBN-10: 1-4027-2247-8. ISBN-13: 978-1-4027-2247-9.
- Brain Boosters. Foods And Drugs That Make You Smarter. (A quote from the book: "It's hard to distinguish between the health and anti-aging uses of the smart drugs and nutrients.") By Beverly Potter & Sebastian Orfali. Ronin Publishing. 1993. Paperback, 257 pages. ISBN 0-914171-65-8
- Brain Fitness. Anti-Aging Strategies To Fight Alzheimer's Disease, Supercharge Your Memory, Sharpen Your Intelligence, De-Stress Your Mind, Control Mood

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- Brain Longevity: The Breakthrough Medical Program that Improves Your Mind and Memory. By Dharma Singh Khalsa.
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- Mind Food and Smart Pills. How To Increase Your Intelligence and Prevent Brain Aging. By Ross Pelton. 1986. Paperback, 170pp. ISBN 0-936809-00-0
  - Smart Drugs & Nutrients. How To Improve Your Membory And Increase Your Intelligence Using The Latest Discoveries In Neuroscience. (Many of the substances in this book have life-extending or cell regenerating effects.) By Ward Dean, M.D. and Joh Morgenthaler. B&J Publications. 1990. Paperback, 222pp. ISBN 096271892
  - Smart Drugs II: The Next Generation : New Drugs and Nutrients to Improve Your Memory and Increase Your Intelligence. By Ward Dean (M.D.), John Morgenthaler, Steven Wm Fowkes. Smart Publications. 1993. Paperback, 287 pages. ISBN 0-9627418-7-6
- Your Personal Life-Extension Program. A Practical Guide to the New Science That Can Make You Stronger, Smarter, Sexier, More Energetic, and More Youthful. *Chapter 14: Therapies to Improve Memory and Intelligence.* By Saul Kent. Morrow. 1985. Hardcover, 384 pages. ISBN 0-688-00629-9

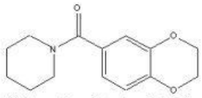
Ampakines

Ampakines are a new class of modified benzamide compounds known to enhance attention span and alertness. Their action is theorized to be due to facilitation of transmission at cortical synapses that use glutamate as neurotransmitter. This in turn may promote plasticity at the synapse, which could translate into better cognitive performance. The ampakines take their name from the glutamatergic AMPA receptor, which they strongly interact with.

Unlike earlier stimulants (e.g. caffeine, methylphenidate (Ritalin®), the Amphetamine) they do not seem to have unpleasant, long-lasting side effects such as sleeplessness. They are currently (2005) investigated as potential treatment for a range of conditions involving mental disability such as Alzheimer's disease, Parkinson's disease, schizophrenia or neurological disorders as Attention Deficit Hyperactivity Disorder (ADHD), among others. In a 2006 study they were shown to have an effect after they had left the body, continuing to enhance learning and memory.

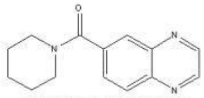
Some examples include: CX-516 (Ampalex), CX546, CX614 and CX717.

Structure



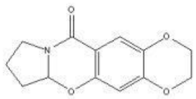
1-(1,4-benzodioxan-6-ylcarbonyl) piperidine

CX546



1-(quinoxalin-6-ylcarbonyl)piperidine

CX516



2H,3H,6aH-pyrrolidino[2",1"-3',2']1,3-oxazino[6',5'-5,4]benzo[e]1,4-dioxan-10-one

CX614

Mechanism

Ampakines work by allosterically binding to particular receptors in the brain, called AMPA-type glutamate receptors. This boosts the activity of glutamate, a neurotransmitter, and makes it easier to encode memory and to learn. In addition, some members of the Ampakine family of drugs may also increase levels of trophic factors such as Brain Derived Neurotrophic Factor (BDNF).

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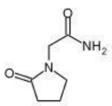
See also

- Nootropic
- Stimulants

Substances of the piracetam group



Piracetam **Systematic (IUPAC) name**

2-oxo-1-pyrrolidineacetamide

Identifiers

CAS number rn=1" href="http://www.nlm.nih.gov/cgi/mesh/2006/MB_cgi?term=7491-74-9&rn=1"> 7491-74-9

ATC code **N06**BX03

Chemical data

Formula C***6***H***10***N***2***O***2***

Mol. weight 142.156 g/mol

Pharmacokinetic data

Bioavailability ~100 %

Half life 4-5 hours

Excretion Urinary

Therapeutic considerations

Legal status UK: POM; legal to import
Orphan drug

Routes Oral and parenteral

Piracetam (brand name: *Nootropil*®, Myocalm®), is a cerebral function regulating drug which is claimed to be able to enhance cognition as well as slow down brain aging. Piracetam's chemical name is 2-oxo-pyrrolidone, or 2-oxo-1-pyrrolidine acetamide. Piracetam is a cyclic derivative of GABA. It is one of the racetams, and is similar to the amino acid pyroglutamate. Though rare in the United States, Piracetam is commonly prescribed in Europe for a variety of conditions.

Effects

Several meta-reviews of literature on Piracetam indicate that Piracetam increases performance on a variety of cognitive tasks among dyslexic children, though this may reflect its enhancement of cross-hemispheric communication and of cognitive function in general, rather than a specific improvement in whatever causes dyslexia. Piracetam also seems to inhibit brain damage caused by a variety of factors including hypoxia and excessive alcohol consumption.

Piracetam has been studied in an extensive number of clinical experiments, mostly focusing on dyslexic children, and some believe that understanding the mechanism it works through can teach us about the role of inter-hemispheric communication in the brain.

Mechanisms of action

The mechanisms of action of Piracetam are quite broad. Piracetam is understood to work by stimulating the cerebral cortex as well as by increasing the rate of metabolism and the energy levels of neurons. It possibly facilitates movement of information between the brain's two hemispheres via the corpus callosum, and improves the function of the neurotransmitter acetylcholine via muscarinic cholinergic (ACh) receptors which are implicated in memory processes. Furthermore, Piracetam may have an effect on NMDA glutamate receptors which are involved with learning and memory processes. Finally, Piracetam may exert its global effect on brain neurotransmission via modulation of ion channels (i.e., Ca^{2+}, K^{+}).

History

Piracetam was first synthesized in 1964 by scientists at the Belgian pharmaceutical company UCB led by Dr Corneliu E. Giurgea. The drug was the first of the so-called nootropics ("smart drugs" or "cognitive enhancers"), that is, substances which purportedly enhance mental performance. The term nootropic was coined by Giurgea. Nootropil was launched clinically by UCB in the early 1970s and remains an important product of that company in Europe.

Approval and usage

Piracetam is primarily used in Europe. Piracetam is legal to import into the United Kingdom for personal use with or without prescription as with other prescription-only

drugs. As of June of 2006, piracetam is not regulated in the United States (it is neither a controlled substance nor a prescription drug).

Dosage

Piracetam is usually supplied in 800 mg tablets or capsules. The recommended dosage varies based on the indication, usually ranging from 1.6-9.6 grams daily (2-12 pills daily). Some people report faster results when taking 1-2 pills every hour for 4-6 hours or taking 4-8 pills at once for the first few days to notice an effect.

It has been studied up to 45 grams daily without major side effects.

It has no known LD-50 in humans when taken orally.

In the US, and possibly other countries in which Piracetam is unregulated, it is often sold in bulk as a powder. It is up to the user to decide how they want to ingest said powder; orange juice is frequently cited as a good mixer to mask the taste.

Contraindications

Piracetam is contra-indicated in patients with severe renal impairment (renal creatinine clearance of less than 20 ml per minute), hepatic impairment and to those under 16 years of age. It is also contraindicated in patients with cerebral haemorrhage and in those with hypersensitivity to piracetam, other pyrrolidone derivatives or any of the excipients .

Special warnings and precautions for use

Due to the effect of piracetam on platelet aggregation, caution is recommended in patients with underlying disorders of haemostasis, major surgery or severe haemorrhage.

Abrupt discontinuation of treatment should be avoided as this may induce myoclonic or generalised seizures in some myoclonic patients.

As piracetam is almost exclusively excreted by the kidneys caution should be exercised in treating patients with known renal impairment. In renally impaired and elderly patients, an increase in terminal half-life is directly related to renal function as measured by creatinine clearance. Dosage adjustment is therefore required in those with mild to moderate renal impairment and elderly patients with diminished renal function.

Undesirable effects

Following adverse experiences (very rare usually occurring in 1 out of 1,000 people) were reported for piracetam with a statistically significantly higher incidence than placebo. Incidences are given for piracetam versus placebo treated patients.

Central and peripheral nervous system disorders: hyperkinesia (1.72 versus 0.42 %)

Metabolic and nutritional disorders: weight gain (1.29 versus 0.39 %)

Psychiatric disorders: nervousness (1.13 versus 0.25 %), somnolence (0.96 versus 0.25 %), depression (0.83 versus 0.21 %)

Body as a whole - general disorders: asthenia (0.23 versus 0.00 %)

Post-marketing experiences have reported the following undesirable effects:

Ear and labyrinth (inner ear) disorders: vertigo

Gastrointestinal disorders: abdominal pain, upper abdominal pain, diarrhoea, nausea, vomiting

Immune system disorders: anaphylactoid reaction, hypersensitivity, multiple chemical sensitivity
Nervous system disorders: ataxia, impaired balance, aggravated epilepsy, headache, insomnia, somnolence
Psychiatric disorders: agitation, anxiety, confusion, hallucination
Skin and subcutaneous tissue disorders: angioneurotic oedema, dermatitis, pruritus, urticaria, rash

See also

- Nootropic

Parasympathomimetics

A *parasympathomimetic* is a drug or poison that acts by stimulating or *mimicking* the parasympathetic nervous system (PNS). These chemicals are also called cholinergics because acetylcholine (ACh) is the neurotransmitter used by the PNS. Chemicals in this family can act by either directly stimulating the nicotinic or muscarinic receptors, or they can act indirectly by inhibiting cholinesterase, promoting acetylcholine release, or other mechanisms. Some Chemical weapons such as sarin or VX, Non-lethal riot control agents such as tear gas, and insecticides such as Diazinon fall into this category.

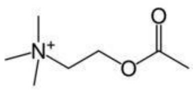
Pharmaceuticals

- Direct acting
  - Choline Esters
    - Acetylcholine
    - Bethanechol
    - Carbachol
  - Plant Alkaloids
    - Nicotine
    - Muscarine
    - Pilocarpine
- Indirect acting
  - Reversible Cholinesterase Inhibitors
    - Donepezil
    - Edrophonium
    - Neostigmine
    - Physostigmine
    - Pyridostigmine
    - Tacrine
  - Irreversible Cholinesterase Inhibitors
    - Echothiophate
    - Isoflurophate
    - Malathion
  - Drugs that promote ACh release
    - Cisapride
    - Metoclopramide
  - Drugs that work by other mechanisms
    - Sildenafil

Sources

Brenner, G. M. (2000). Pharmacology. Philadelphia, PA: W.B. Saunders Company. ISBN 0-7216-7757-6

Anticholinesterases

 Acetylcholine

A *cholinesterase inhibitor* or *anticholinesterase* is a chemical that inhibits a cholinesterase enzyme from breaking down acetylcholine, so increasing both the level and duration of action of the neurotransmitter acetylcholine.

Uses

Anticholinesterases occur naturally as venoms and poisons, are used as weapons in the form of nerve agents, and are used medicinally to treat diseases such as myasthenia gravis and Alzheimer's disease, and as an antidote to anticholinergic poisoning. In myasthenia gravis, they are used to increase neuromuscular transmission.

Examples

reversible inhibitor

Compounds which function as reversible competitive or noncompetitive inhibitors of cholinesterase are those most likely to have therapeutic uses. These include:

- Organophosphates
  - metrifonate
- Carbamates
  - physostigmine

neostigmine
pyridostigmine
ambenonium
demarcarium
rivastigmine

- Phenanthrine derivatives
  - galantamine
- Piperidines
  - donepezil, also known as E2020
- Tacrine, also known as tetrahydroaminoacridine (THA')
- Edrophonium

quasi-irreversible inhibitor

Compounds which function as quasi-irreversible inhibitors of cholinesterase are those most likely to have use as chemical weapons or pesticides. These include:

- Organophosphates
  - echothiophate

diisopropyl fluorophosphate

- cyclosarin
- sarin
- soman
- tabun
- VX
- VE
- VG
- VM

  - diazinon

malathion
parathion

- Carbamates
  - aldicarb

bendiocarb
bufencarb
carbaryl
carbendazim
carbetamide
carbofuran
chlorbufam
chloropropham
ethiofencarb
formetanate
methiocarb
methomyl
oxamyl
phenmedipham
pinmicarb
pirimicarb
propamocarb

propham
propoxur

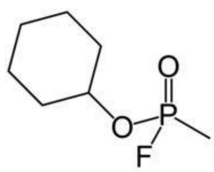
Effects

Some major effects of anticholinesterase:

Actions on the autonomic nervous system, that is parasympathetic nervous system will cause bradycardia, hypotension, hypersecretion, bronchoconstriction, GIT hypermotility, and decrease intraocular pressure.

Actions on the neuromuscular junction will result in prolonged muscle contraction.

Cyclosarin



Discovery

Discovered by Dr. Gerhard Schrader

Discovered in 1949

Chemical Characteristics

Chemical Name (fluoro-methyl-phosphoryl)oxycyclohexane

Chemical Family Fluorinated organophosphorous compound

Chemical formula C7H14FO2P

Airborne Exposure Limit 0.0001 mg/m3

Boiling point 239 °C (462 °F)

Freezing/Melting point -30 °C (-22 °F)

Vapor pressure at 25 °C

Flash point 94 °C (201 °F)

Vapor relative density (air=1) 6.2

Liquid Density 1.1278 g/cc @ 25 °C

Solubility in Water Almost insoluble

Appearance and color Colorless liquid. Odor sweet, musk, peaches, shellac

Cyclosarin or *GF* (Cyclohexyl methylphosphonofluoridate) is an extremely toxic substance that is one of the world's most dangerous weapons of war. It is the most obscure member of the G-series family of nerve agents, a group of chemical weapon discovered and synthesized by a German team, led by Dr. Gerhard Schrader, during or soon after World War II.

As a chemical weapon, it is classified as a weapon of mass destruction by the United Nations according to UN Resolution 687, and its production and stockpiling was outlawed by the Chemical Weapons Convention of 1993.

Chemical characteristics

Like its predecessor, sarin, cyclosarin is a liquid organophosphate nerve agent. Its physical characteristics are quite different from sarin, however.

At room temperature, cyclosarin is a colorless liquid whose odor has been variously described as sweet and musty, and resembling peaches or shellac. Unlike sarin, cyclosarin is a persistent liquid, meaning that it has a low vapor pressure, and therefore evaporates relatively slowly: about 69 times more slowly than sarin and 20 times more slowly than water. Its military value is therefore much greater as a liquid chemical weapon.

Also unlike sarin, cyclosarin is flammable, with a flash point of 94°C (201 °F).

Historical notes

From **CBWInfo.com**

Cyclosarin was first synthesized during World War II as part of the systematic study of organophosphates undertaken by the Germans after their potential military utility was identified. It was again looked at in the early 1950's by both the United States and Great Britain as they undertook a systematic study of potential nerve agents (some U.S. sources suggest that interest in GF was stimulated by work undertaken in "another country"). However, the higher cost of the precursors for GF relative to those for GB along with its lower toxicity prevented it from being chosen for manufacture. Iraq is the only country in which large amounts of cyclosarin have ever been produced for use as a chemical warfare agent. Also Iraqis used sarin and cyclosarin as a mixture against Iran in 1986-1988. As with most issues surrounding the Iraqi chemical weapons programs, the basis for their decision to produce GF is somewhat unclear. However, it seems likely that the choice was driven by a combination of a desire for a more persistent agent combined with problems with obtaining alcohol precursors for sarin (due to an embargo). As noted above, Iraq also fielded weapons filled with mixtures of sarin and cyclosarin. These mixtures appear to have been produced in part for purposes of increasing persistence and in part because of raw material issues.

Munitions

Binary weapons

Like other nerve agents, Cyclosarin can be shipped in binary munitions.

A cyclosarin binary weapon would most likely contain methyphosphonyldifluoride in one capsule with the other capsule containing either cyclohexanol or a mixture of cyclohexylamine and cyclohexanol.

GB-GF Mixtures

According to CBWInfo.com, Iraq fielded munitions filled with a mixture of GB (sarin) and GF (cyclosarin). Tests on mice indicated that GB-GF mixtures have a relative toxicity between GF and GB.

Insecticide

An *insecticide* is a pesticide used against insects in all developmental forms. They include ovicides and larvicides used against the eggs and larvae of insects. Insecticides are used in agriculture, medicine, industry and the household. The use of insecticides is believed to be one of the major factors behind the increase in agricultural productivity in the 20th century. Nearly all insecticides have the potential to significantly alter ecosystems; many are toxic to humans; and others are concentrated in the food chain. It is necessary to balance agricultural needs with environmental and health issues when using them.

Classes of agricultural insecticides

The classification of insecticides is done in several different ways:

- Systemic insecticides are incorporated by treated plants. Insects ingest the insecticide while feeding on the plants.
- Contact insecticides are toxic to insects brought into direct contact. They most often applied through aerosol distribution.
- Natural insecticides, such as nicotine and pyrethrum, are made by plants as defences against insects.
- Inorganic insecticides are manufactured with metals and include arsenates copper- and fluorine compounds, which are now seldom used, and sulfur, which is commonly used.
- Organic insecticides are synthetic chemicals which comprise the largest numbers of pesticides available for use today.
- Mode of action -- how the pesticide kills or inactivates a pest -- is another way of classifying insecticides. Mode of action is important in predicting whether an insecticide will be toxic to unrelated species such as fish, birds and mammals.

Classes of insecticides, a short history

A series of classes of insecticides have existed, as time progressed one class has largely replaced the one before it. These trends in the classes of compounds in some ways has mirrored the development of chemical warfare agents.

Heavy metals, eg lead, mercury, arsenic and plant toxins such as nicotine have been used for many years. Various plants have been used as folk insectides for centuries, including tobacco and pyrethrum.

Chlorine based agents, with the rise of the modern chemical industry it was possible for form organochlorides. The substances used in chemical warfare tend to be more potent electrophiles than those used as insecticides. For instance mustard gas (sulfur mustard, HD) is a potent alklating agent which uses neighbouring group participation of the sulfur to make the alkyl chloride a stronger electrophile. An organochlorine insecticide such as DDT or lindane does not directly kill the insect. It is likely that the chlorine is used to tune the lipophilicity of the compound, and to alter the shape and electrostatic effects involved in the interactions of the insecticide and the biomolecules in the target organism. For instance DDT works by opening the sodium channels in the nerve cells of the insect.

The next large class was the organophosphates, both the insecticides and the chemical warfare agents (such as sarin, tabun, soman and VX) work in the same way. All these compounds bind to the neurotransmitter acetylcholinesterase and other cholinesterases. This results in disruption of nervous impulses, killing the insect or interfering with its ability to carry on normal functions. Carbamate insecticides have similar toxic mechanisms but have a much shorter duration of action and are somewhat less toxic on that basis.

To mimic the insecticidal activity of the natural compound pyrethrum another class of pesticides, pyrethroid pesticides, have been developed. These are are nonpersistent and much less acutely toxic than organophosphates and carbamates.

Recent efforts to reduce broad spectrum toxins added to the environment have brought biological insecticides back into vogue. An example is the development and increase in use of Bacillus thuringiensis, a bacterial disease of Lepidopterans and some other insects. It is used as a larvicide against a wide variety of caterpillars. Because it has little effect on other organisms, it is considered more environmentally friendly than synthetic pesticides. The toxin from Bacillus thuringiensis (Bt toxin) has been incorporated directly into plants through the use of genetic engineering.

Environmental effects

One of the bigger drivers in the development of new insecticides has been the desire to replace toxic and irksome insecticides. The notorious DDT was introduced as a safer alternative to the lead and arsenic compounds which had been used before. It is the case that when used under the correct conditions that almost any chemical substance is 'safe', but when used under the wrong conditions most insecticides can be a threat to health and/or the environment.

Some insecticides have been banned due to the fact that they are persistent toxins which have adverse effects on animals and/or humans. A classic example which is often quoted is that DDT is an example of a widely used (and maybe misused) pesticide. One of the better known impacts of DDT is to reduce the thickness of the egg shells on predatory birds. The shells sometimes become too thin to be viable, causing reductions in bird populations. This

occurs with DDT and a number of related compounds due to the process of bioaccumulation, wherein the chemical, due to its stability and fat solubility, accumulates in organisms fat. Also, DDT may biomagnify which causes progressively higher concentrations in the body fat of animals farther up the food chain. The near-worldwide ban on agricultural use of DDT and related chemicals has allowed some of these birds--such as the peregrine falcon--to recover in recent years. A number of the organochlorine pesticides have been banned from most uses worldwide and globally they are controlled via the Stockholm Convention on Persistent Organic Pollutants. These include: aldrin, chlordane, DDT, dieldrin, endrin, heptachlor, mirex and toxaphene.

While the overuse of DDT lead to a reduction in its use, opponents of traditional environmentalism often cite it as an example of environmentalism going too far and interfering with malaria eradication, going so far as to estimate the cost of human lives resulting from the DDT ban; for instance the novelist Michael Crichton states in his bestselling book, State of Fear:

"Since the ban, two million people a year have died unnecessarily from malaria, mostly children. The ban has caused more than fifty million needless deaths. Banning DDT killed more people than Hitler."

This accusation, while sensational, is erroneous, as no ban exists on the use of DDT for eradication of malaria or any other mosquito borne disease. Groups fighting malaria have praised the ban on agricultural use of DDT, since it reduces the rate with which mosquitoes become resistant to DDT, which is the main reason it is not used more often to fight malaria:

"The outcome of the treaty is arguably better than the status quo going into the negotiations over two years ago. For the first time, there is now an insecticide which is restricted to vector control only, meaning that the selection of resistant mosquitoes will be slower than before.".

In fact, according to Agricultural production and malaria resurgence in Central America and India, Chapin, Georgeanne & Robert Wasserstrom, Nature, Vol. 293, 1981, page 183), the lives actually saved due to banning agricultural use of DDT can be estimated:

"Correlating the use of DDT in El Salvador with renewed malaria transmission, it can be estimated that at current rates each kilo of insecticide added to the environment will generate 105 new cases of malaria."

Alternative insecticides have had to be used as an alternative to DDT because the population of insects have become resistant to DDT. Most of the newer insecticides are more specific in their actions and are designed to break down into non-toxic components within a few days of application. Nonetheless, misuse of insecticides remains an environmental and economic issue. For example, in Bangladesh most of the insecticide applications by rice farmers are apparently unnecessary.

Application methods for household insecticides

Integrated pest management or IPM in the home begins with restricting the availability to insects of three vital commodities: shelter, water and food. If insects become a problem despite such measures then it is wise to control them using the safest possible methods, targeting the approach that is used to the pest that is present in the household environment[1].

Insect repellent, commonly referred to as "bug spray", comes in a plastic bottle or aerosol can. Applied to clothing, arms, legs, and other extremities, the use of these products will tend to ward off nearby insects. This is not an insecticide.

Insecticide used for killing pests—most often insects, and arachnids—primarily comes in an aerosol can, and is sprayed into the air or a nest as a means of killing the animal. Fly sprays will kill house flies, blowflies, ants, cockroaches and other insects and also spiders. Other preparations are granules or liquids that are formulated with bait that is eaten by insects. For many household pests bait traps are available that contain the pesticide and either pheromone or food baits. Crack and crevice sprays are applied into and around openings in houses such as baseboards and plumbing. Pesticides to control termites are often injected into and around the foundations of homes.

Active ingredients of many household insecticides include permethrin and tetramethrin, which act on the nervous system of insects and arachnids.

Bug sprays should be used in well ventilated areas only, as the chemicals contained in the aerosol and most insecticides can be harmful or deadly to humans and companion animals. All insecticide products including solids, baits and bait traps should be applied such that they are out of reach of wildlife, companion animals and children.

Individual insecticides

Chlorinated

- Camphechlor
- DDT
- Hexachlorocyclohexane
  - gamma-Hexachlorocyclohexane

Lindane

- Methoxychlor

Pentachlorophenol

TDE

Category:Cyclodiene

- Aldrin

Chlordane

Chlordecone

Dieldrin

Endosulfan

Endrin

Heptachlor

Mirex

Organophosphorus

- Acephate
Azinphos-methyl
Bensulide
Chlorethoxyfos
Chlorpyrifos
Chlorpyriphos-methyl
Diazinon
Dichlorvos (DDVP)
Dicrotophos
Dimethoate
Disulfoton
Ethoprop
Fenamiphos
Fenitrothion
Fenthion
Fosthiazate
Malathion
Methamidophos
Methidathion
Methyl-parathion
Mevinphos
Naled
Omethoate
Oxydemeton-methyl
Parathion
Phorate
Phosalone
Phosmet
Phostebupirim
Pirimiphos-methyl
Profenofos
Terbufos
Tetrachlorvinphos
Tribufos
Trichlorfon

Carbamates

- Aldicarb
Carbofuran
Carbaryl

Methomyl
2-(1-Methylpropyl)phenyl methylcarbamate

Pyrethroids

- Allethrin
Bifenthrin
Deltamethrin
Permethrin
Resmethrin
Sumithrin
Tetramethrin
Tralomethrin
Transfluthrin

Plant toxin derived

- Derris (rotenone)
Pyrethrum
Neem (Azadirachtin)

- Nicotine
- Caffeine

Nerve agents

Nerve agents (also known as *nerve gases*, though these chemicals are liquid at room temperature) are a class of phosphorus-containing organic chemicals (organophosphates) that disrupt the mechanism by which nerves transfer messages to organs. The disruption is caused by blocking acetylcholinesterase, an enzyme that normally relaxes the activity of acetylcholine, a neurotransmitter. As chemical weapons, they are classified as weapons of mass destruction by the United Nations according to UN Resolution 687, and their production and stockpiling was outlawed by the Chemical Weapons Convention of 1993; the Chemical Weapons Convention officially took effect on April 29, 1997.

Poisoning by a nerve agent leads to contraction of pupils, profuse salivation, convulsions, involuntary urination and defecation, and eventual death by asphyxiation as control is lost over respiratory muscles. Some nerve agents are readily vaporized or aerosolized and the primary portal of entry into the body is the respiratory system. Nerve agents can also be absorbed through the skin, requiring that those likely to be subjected to such agents wear a full body suit in addition to a respirator.

Biological effects

As their name suggests, nerve agents attack the nervous system of the human body. All such agents function the same way: by interrupting the breakdown of the neurotransmitters that signal muscles to contract, preventing them from relaxing.

Initial symptoms following exposure to sarin (and other nerve agents) are a runny nose, tightness in the chest and constriction of the pupils. Soon after, the victim will then have difficulty breathing, and will experience nausea and drooling. As the victim continues to lose control of his or her bodily functions, he or she will involuntarily salivate, lacrimate, defecate, urinate and vomit ("SLUD" syndrome). This phase is followed by twitching and jerking, and ultimately the victim will become comatose and suffocate as a consequence of convulsive spasms.

The effects of nerve agents are very long lasting and cumulative (increased successive exposures), and survivors of nerve agent poisoning almost invariably suffer chronic neurological damage.

Mechanism of action

When a normally functioning motor nerve is stimulated it releases the neurotransmitter acetylcholine, which transmits the impulse to a muscle or organ. Once the impulse is sent, the enzyme acetylcholine esterase immediately breaks down the acetylcholine in order to allow the muscle or organ to relax.

Nerve agents disrupt the nervous system by inhibiting the enzyme acetylcholine esterase by forming a covalent bond with the site of the enzyme where acetylcholine normally undergoes hydrolysis (breaks down). The result is that acetylcholine builds up and continues to act so that any nerve impulses are continually transmitted, and muscle contractions do not stop.

This same action also occurs at the gland and organ levels, resulting in uncontrolled drooling, tearing of the eyes (lacrimation), and excess production of mucous from the nose (rhinorrhea).

Antidotes

Atropine and related anticholinergic drugs act as antidotes to nerve agent poisoning because they block acetylcholine receptors, but they are poisonous in their own right. While they will save the life of a person affected with nerve agents, that person may be incapacitated briefly or for an extended period of time, depending on the amount of exposure. Atropine for field use by military personnel is often loaded in an autoinjector, for ease of use in stressful conditions.

Pralidoxime chloride, also known as 2-Pam chloride, is also used as an antidote. Rather than counteracting the initial effects of the nerve agent on the nervous system like atropine, pralidoxime chloride actually neutralizes the nerve agent in the bloodstream. Though safer to use, it takes a longer time to have an effect.

Classes

There are two main classes of nerve agents. The members of the two classes share similar properties, and are given both a common name (such as sarin), and a two-character NATO identifier (such as GB).

G-Series

The G-series, thus named because German scientists first synthesized them. All of the compounds in this class were discovered and synthesized during or soon after World War II, led by Dr. Gerhard Schrader (later under the employment of I.G. Farben).

This series is the first and oldest family of nerve agents. The first nerve agent ever synthesised was GA (tabun) in 1936. GB (sarin) was discovered next in 1938, followed by GD (soman) in 1944 and finally the more obscure GF (cyclosarin) in 1949.

V-Series

The V-series is the second family of nerve agents (the V apparently standing for "venomous"), and also contains four members: VE, VG, VM, VX. The most studied agent in this family, VX, was invented in the 1950s at Porton Down in the United Kingdom. The other agents in this series have not been studied extensively, and information about them is limited. It is known, however, that the V-series agents are about 10 times more toxic than the G-agent sarin (GB).

All of the V-agents are persistent agents, meaning that these agents do not degrade or wash away easily, and can therefore remain on clothes and other surfaces for long periods. In use, this allows the V-agents to be used to blanket terrain to guide or curtail the movement of enemy ground forces. The consistency of these agents is similar to oil; as a result, the contact hazard for V-agents is primarily - but not exclusively - dermal.

Novichok Agents

The Novichok series was a new series of organophosphate agents developed in the Soviet Union. The advantage to using new agents was that they hadn't been seen before and hence there were no specific treaties, protective gear or detectors developed to defend against their use.

Insecticides

A number of insecticides, such as dichlorvos, malathion and parathion are nerve agents. The metabolism of insects is sufficiently different from mammals that these compounds are considered innocuous for humans and their food animals; but there is considerable concern about the effects of long-term exposure to these chemicals by farm workers and animals alike.

History

The discovery of nerve agents

This first class of nerve agents, the so-called G-Series, was accidentally discovered in Germany on December 23, 1936 by a research team headed by Dr. Gerhard Schrader. Since 1934, Schrader had been in charge of a laboratory in Leverkusen to develop new types of insecticides for IG Farben. While working toward his goal of improved insecticide, Schrader experimented with numerous fluorine-containing compounds, eventually leading to the preparation of tabun.

In experiments, tabun was extremely potent against insects: as little as 5 ppm of tabun killed all the leaf lice he used in his initial experiment. In January 1937, Schrader observed the effects of nerve agents on human beings first-hand when a drop of tabun spilled onto a lab bench. Within minutes he and his laboratory assistant began to experience miosis (contraction of the pupils of the eyes), dizziness, and severe shortness of breath. It took them three weeks to recover fully.

In 1935 the Nazi leadership had passed a decree that required all inventions of possible military significance to be reported to the Ministry of War, so in May of 1937 Schrader sent a sample of tabun to the chemical warfare (CW) section of the Army Weapons Office in Berlin-Spandau. Dr. Schrader was summoned to the Wehrmacht chemical lab in Berlin to give a demonstration, after which Schrader's patent application and all related research was classified. Colonel Rüdiger, head of the CW section, ordered the construction of new laboratories for the further investigation of tabun and other organophosphate compounds, and Schrader soon moved to a new laboratory at Wuppertal-Elberfeld in the Ruhr valley to continue his research in secret throughout World War II.

Three of the most widely known agents, sarin (GB), soman (GD), and tabun (GA) were also developed during this period for use as chemical warfare agents, but were not used in combat. Cyclosarin (GF) was developed somewhat later, in 1949, by the same team. The prefix "G" was used in the names of all the chemicals because they were of German origin[1].

The Nazi mass production of tabun

In 1939, a pilot plant for tabun production was set up at Munster-Lager, on Luneberg heath near the German Army proving grounds at Raubkammer. In January 1940, construction began on a secret plant, code named "Hochwerk" (High factory), for the production of tabun at Dyernfurth-am-Oder (now Brzeg Dolny in Poland), on the Oder River 40 km (24.9 miles) from Breslau (now WrocBaw) in Silesia.

The plant was large, covering an area of 2.4 by 0.8 km (1.5 by 0.5 miles), and was completely self-contained, synthesizing all intermediates as well as the final product, tabun. The factory even had an underground plant for filling munitions, which were then stored at Krappitz (now Krapowice) in Upper Silesia. The plant was operated by Anorgana GmbH, a subsidiary of IG Farben, as were all other chemical weapon agent production plants in Germany at the time.

Because of the plant's deep secrecy and the difficult nature of the production process, it took from January 1940 until June 1942 for the plant to become fully operational. Many of tabun's chemical precursors were so corrosive that reaction chambers not lined with quartz or silver soon became useless. Tabun itself was so hazardous that the final processes had to be performed while enclosed in double glass-lined chambers with a stream of pressurized air circulating between the walls.

3,000 German nationals were employed at Hochwerk, all equipped with respirators and clothing constructed of a poly-layered rubber/cloth/rubber sandwich that was destroyed after the tenth wearing. Despite all precautions, there were over 300 accidents before production even began, and at least 10 workers died during the 2.5 years of operation. Some incidents cited in A Higher Form of Killing: The Secret History of Chemical and Biological Warfare are as follows:

- Four pipe fitters had liquid tabun drain onto them; they died before their rubber suits could be removed.
- A worker had 2 liters of tabun pour down the neck of his rubber suit; he died within 2 minutes.
- Seven workers were hit in the face with a stream of tabun of such force that the liquid was forced behind their respirators; only two survived despite heroic resuscitation measures.

The plant produced between 10,000 and 30,000 tons of tabun before its capture by the Soviet Army [1].

Nerve agents in Nazi Germany

In mid-1939, sarin was invented, and the formula for the agent was passed to the Chemical Warfare section of the German Army Weapons Office, which ordered that it be brought into mass production for wartime use. A number of pilot plants were built, and a high-production facility was under construction (but was not finished) by the end of World War II. Estimates for total sarin production by Nazi Germany range from 500 kg to 10 tons.

During that time, German intelligence believed that the Allies also knew of these compounds, assuming that because these compounds were not discussed in the Allies' scientific journals information about them was being suppressed. Though sarin, tabun and soman were incorporated into artillery shells, the German government ultimately decided not to use nerve agents against Allied targets, because they feared a devastating Allied retaliatory nerve agent deployment. However, the Allies didn't learn of these agents until shells filled with them were captured towards the end of the war.

This is detailed in Joseph Borkin's book The Crime and Punishment of IG Farben:

Speer, who was strongly opposed to the introduction of tabun, flew Otto Ambros, I.G.'s authority on poison gas as well as synthetic rubber, to the meeting. Hitler asked Ambros, "What is the other side doing about poison gas?" Ambros explained that the enemy, because of its greater access to ethylene, probably had a greater capacity to produce mustard gas than Germany did. Hitler interrupted to explain that he was not referring to traditional poison gases: "I understand that the countries with petroleum are in a position to make more [mustard gas], but Germany has a special gas, tabun. In this we have a monopoly in

Germany." He specifically wanted to know whether the enemy had access to such a gas and what it was doing in this area. To Hitler's disappointment Ambros replied, "I have justified reasons to assume that tabun, too, is known abroad. I know that tabun was publicized as early as 1902, that Sarin was patented, and that these substances appeared in patents. (...) Ambros was informing Hitler of an extraordinary fact about one of Germany's most secret weapons. The essential nature of tabun and sarin had already been disclosed in the technical journals as far back as 1902, and I.G. had patented both products in 1937 and 1938. Ambros then warned Hitler that if Germany used tabun, it must face the possibility that the Allies could produce this gas in much larger quantities. Upon receiving this discouraging report, Hitler abruptly left the meeting. The nerve gases would not be used, for the time being at least, although they would continue to be produced and tested.

—Joseph Borkin, The Crime and Punishment of IG Farben

The secret gets out

After World War II, the Allies recovered German artillery shells containing the three German nerve agents of the day, prompting further research into nerve agents by the former Allies. In 1952, researchers in Porton Down, England invented the VX nerve agent, but soon abandoned the project. In 1958 the British government traded their VX technology with the United States of America in exchange for information on thermonuclear weapons; by 1961 the US was producing large amounts of VX, and performed its own nerve agent research. This research produced three more agents; the four agents (VE, VG, VM, VX) are collectively known as the "V-Series" class of nerve agents.

Since World War II

To date, nerve agents have not been used in warfare on a large scale. Iraq briefly used chemical weapons, including nerve agents, during the Iran-Iraq war of 1981-1988; the Kurdish village of Halabja was exposed to chemical weapons, reportedly including nerve agents. Nerve agents were not used by Iraq in the Gulf War, though a number of U.S. and UK personnel were exposed to them when the Khamisiyah chemical depot was destroyed. This and the widespread use of anticholinergic drugs as a protective treatment against nerve gas attack has been proposed as a possible cause of Gulf war syndrome.

One of the most widely publicised uses of nerve agents was the 1995 terrorist attack in which operatives of the group Aum Shinrikyo released sarin into the Tokyo subway system.

Ocean Disposal of Chemical Weapons

In 1972, The United States Congress banned the practice of disposing chemical weapons into the ocean. However 32,000 tons of nerve and mustard agents had already been dumped into the ocean waters off of the United States by the U.S. Army. According to a 1998 report created by William Brankowitz, a deputy project manager in the U.S. Army Chemical Materials Agency, the Army created at least 26 chemical weapons dumpsites in the ocean off

of at least 11 states on both the west and east coasts. Additionally due to poor records, currently they only know the rough whereabouts of half of them.

It is unknown how these dumps of chemical weapons have affected the ocean ecology—it may be responsible for some of the decline in fish populations over the past decades, but no evidence has yet proved a causal relationship between dumping and fish population decline. The steel containers they are contained within face a variable rate of decay and no one is really certain where or how deep they were dumped. If a nerve agent leaks into the ocean, it can last up to six weeks, during which time it will kill everything it touches before it breaks down into its nonlethal chemical components.

Popular Culture

As a weapon of fear and terror, nerve agents are quickly becoming a staple in the plots of television, cinema, and video games. In most implementations of this plot, a shadowy terrorist organization obtains a quantity of nerve agent and threatens to release it in a population center.

A fictional nerve agent, ZV, is an integral part of the story line for John Lange's (a pseudonym of Michael Crichton) 1972 novel Binary. The effects of this agent were the same as the V-series agents and the book mentions these other agents although it does not mention other existing binary nerve agents such as the G-series or VX.

A nerve agent later featured in the 1986 film Aliens, in which the character Vasquez suggests employing a fictional nerve agent, CN-20. Later, nerve agents appeared in two 1996 action movies: The Rock, in which a retired US Marine general blackmails the government by threatening to attack California with "VX gas", and Executive Decision, which prominently featured a fictional nerve agent called "DZ-5". In the 2002 movie XXX, a terrorist group called Anarchy-99 produces a fictitious binary nerve agent called "Silent Night," which decomposed and became harmless when passed through water. In the movie Saw II, sarin is the nerve agent that the Jigsaw Killer uses as part of his game.

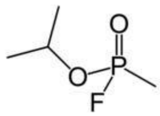
This plot device was adopted by video game designers as well. For example, Tom Clancy's Rainbow Six 3: Raven Shield featured terrorists that attempted to poison the food supply with VX nerve agent. Also, it was the new deadly threat in Syphon Filter: Dark Mirror, where the nerve gas, Project Dark Mirror, was said to blend with oxygen, making it more lethal

Before long, nerve agents began to appear on television. For example, VX was featured in the British television series Spooks as part of a simulated attack on the center of London, and recently, on season 5 of the primetime FOX series, 24, Russian separatists manage to use a fictional, vaporised variant of VX called "Sentox VX-1" on several targets in Los Angeles. The Doctor Who story The Mind of Evil involves the hijacking of a nerve gas missile destined to be destroyed, and in the later story Terror of the Zygons a Scottish village is drugged with a nerve gas agent. Sarin was also featured in a later series of Spooks.

The post-grunge band Seether was first known as "Saron Gas".

1. **^** a b History of Nerve Agents**, Frederick Sidell**

Sarin



Discovered by Gerhard Schrader, Ambrose Rüdiger van der Linde

Discovered in 1938

Chemical Characteristics

Chemical Name 2-(fluoro-methyl-phosphoryl)oxypropane

Chemical Family Fluorinated organophosphorus compound

Chemical formula $C_4H_{10}FO_2P$

NFPA Rating

- Health - 4
- Flammability - 1
- Reactivity - 1

Airborne exposure limit 0.0001 mg/m3

Boiling point 158 °C

Freezing/melting point -56 °C

Vapor pressure 2.9 at 25 °C

Vapor relative density (Air=1) 4.86

Liquid Density

1.0887 g/cm^3 at 25 °C
1.102 g/cm^3 at 20 °C

Solubility in Water Complete

Appearance and color Colorless liquid. Odorless in pure form.

Precursors

Key precursors

methylphosphonyl difluoride
methylphosphonyl dichloride
diisopropyl methylphosphonochloridate

Precursors

Dimethyl methylphosphonate
isopropyl methylphosphonate

Other chemicals

Trimethylphosphite
phosphorus trichloride
triisopropyl phosphite

Except where noted otherwise, data are given for materials in their standard state (at 25 °C, 100 kPa)

Sarin, also known by its NATO designation of *GB* (O-Isopropyl methylphosphonofluoridate) is an extremely toxic substance whose sole application is as a nerve agent. As a chemical weapon, it is classified as a weapon of mass destruction by the United Nations according to UN Resolution 687, and its production and stockpiling was outlawed by the Chemical Weapons Convention of 1993.

Chemical characteristics

Sarin is similar in structure and biological activity to some commonly used insecticides, such as Malathion, and is similar in biological activity to carbamates used as insecticides such as Sevin, and medicines such as Mestinon, Neostigmine, and Antilirium.

At room temperature, sarin is a colourless, odourless liquid. Its relatively high vapor pressure means that it evaporates quickly (about 36 times faster than tabun, another common chemical nerve agent). Its vapor is also colorless and odorless. It can be made more persistent through the addition of certain oils or petroleum products.

Sarin can be used as a binary chemical weapon; its two precursors are methylphosphonyl difluoride and a mixture of isopropyl alcohol and isopropyl amine. The isopropyl amine binds the hydrogen fluoride generated during the chemical reaction.

Shelf life

Sarin has a relatively short shelf life, and will degrade after a period of several weeks to several months. The shelf life may be greatly shortened by impurities in precursor materials. According to the CIA, in 1989 the Iraqis destroyed 40 or more tons of sarin that had decomposed, and that some Iraqi sarin had a shelf life of only a few weeks owing mostly to impure precursors.

Like other nerve agents, Sarin can be chemically deactivated with a strong alkali. Typically an 18 percent aqueous solution of sodium hydroxide is used to destroy Sarin.

Efforts to lengthen shelf life

According to the CIA, nations such as Iraq have tried to overcome the problem of sarin's short shelf life in three ways:

- The shelf life of unitary (i.e., pure) sarin may be lengthened by increasing the purity of the precursor and intermediate chemicals and refining the production process.
- Incorporating a stabilizer chemical called tributylamine. Later this was replaced by diisopropylcarbodiimide (di-c-di), which allowed for GB nerve agent to be stored in aluminum casings.
- Developing binary chemical weapons, where the two precursor chemicals are stored separately in the same shell, and mixed to form the agent immediately before or when the shell is in flight. This approach has the dual benefit of making the issue of shelf life irrelevant and greatly increasing the safety of sarin munitions.

Biological Effects

Like other nerve agents, sarin attacks the nervous system of a living organism.

When a functioning motor nerve is stimulated it releases the neurotransmitter acetylcholine to transmit the impulse to a muscle or organ. Once the impulse has been sent, the enzyme acetylcholinesterase breaks down the acetylcholine in order to allow the muscle or organ to relax.

Sarin is an extremely potent organophosphate compound that disrupts the nervous system by inhibiting the cholinesterase enzyme by forming a covalent bond with the site of the enzyme where acetylcholine normally undergoes hydrolysis. This allows acetylcholine to build up and continue to act so that any nerve impulses are, in effect, continually transmitted.

Initial symptoms following exposure to sarin (and other nerve agents) are a runny nose, tightness in the chest and contraction of the pupils. Soon after, the victim has difficulty breathing and experiences nausea and drooling. As the victim continues to lose control of bodily functions, he vomits, defecates and urinates. This phase is followed by twitching and jerking. Ultimately, the victim becomes comatose and suffocates in a series of convulsive spasms.

Sarin is a highly volatile liquid. Inhalation and absorption through the skin pose a great threat. Even vapour concentrations immediately penetrate the skin. People who absorb a nonlethal dose but do not receive immediate appropriate medical treatment may suffer permanent neurological damage.

Even at very low concentrations, sarin can be fatal. Death may follow in one minute after direct ingestion of about 0.01 milligram per kilogram of body weight if antidotes, typically atropine and pralidoxime, are not quickly administered. Atropine, an acetylcholine inhibitor,

is given to treat the physiological symptoms of poisoning. Pralidoxime can regenerate cholinesterases if administered within approximately five hours.

It is estimated that sarin is more than 500 times as toxic as cyanide.

The short- and long-term symptoms experienced by those affected included:

- bleeding from the nose and mouth

coma
convulsions
death
difficulty breathing
disturbed sleep and nightmares
extreme sensitivity to light
foaming at the mouth
high fevers
influenza-like symptoms
loss of consciousness
loss of memory
nausea and vomiting
paralysis
post-traumatic stress disorder
respiratory problems
seizures
uncontrollable trembling
vision problems, both temporary and permanent

History

The following is the specific history of sarin, which is closely linked to the history of similar nerve agents also discovered in Germany during or soon after World War II. That broader history is detailed in Nerve Agent: History .

Origin

Sarin was discovered in 1938 in Wuppertal-Elberfeld in the Ruhr valley of Germany by two German scientists while attempting to create stronger pesticides; it is the most toxic of the four G-agents made by Germany. The compound, which followed the discovery of the nerve agent tabun, was named in honor of its discoverers: Gerhard *S*chrader, *A*mbros, *R*üdiger and Van der L*IN*de.

Sarin in Nazi Germany During World War II

In mid-1939, the formula for the agent was passed to the Chemical Warfare section of the German Army Weapons Office, which ordered that it be brought into mass production for wartime use. A number of pilot plants were built, and a high-production facility was under

construction (but was not finished) by the end of World War II. Estimates for total sarin production by Nazi Germany range from 500 kg to 10 tons.

Though sarin, tabun and soman were incorporated into artillery shells, Germany ultimately decided not to use nerve agents against Allied targets. German intelligence was unaware that the Allies had not developed similar compounds, and they were concerned that the Allies' ability to reach German targets would prove devastating in a chemical war.

Sarin after World War II

- 1950s (early): NATO adopts sarin as a standard chemical weapon, and both Russia and the United States produce sarin for military purposes.
- The feedstock chemicals required for GB production include: hydrofluoric acid, methylphosphonic dichloride (dichlor) and isopropyl alcohol. Other materials used in the GB manufacturing process included: the stabilizing additive; calcium chloride brine, the refrigerant; and methylene chloride, the heat transfer agent.
- 1953: 20-year old Ronald Maddison, a Royal Air Force engineer from Consett, County Durham, died in human testing of sarin at the Porton Down chemical warfare testing facility in Wiltshire. Maddison had been told that he was participating in a test to "cure the common cold." Ten days after his death an inquest was held in secret which returned a verdict of "misadventure". In 2004 the inquest was reopened and, after a 64-day inquest hearing, the jury ruled that Maddison had been unlawfully killed by the "application of a nerve agent in a non-therapeutic experiment."
- 1956: Regular production of sarin ceased in the United States, though existing stocks of bulk Sarin were re-distilled until 1970.
- 1978: Michael Townley in a Sworn declaration indicates that Sarin was produced by the secret police of the Chile Pinochet dictatorship DINA, by Eugenio Berríos, it indicates that it was used to assassinate the real state archives custodian Renato León Zenteno and the Army Corporal Manuel Leyton.[1]
- 1980-1988: Iraq employed sarin against Iran during the 1980-88 war. During the 1990-91 Gulf War, Iraq still had large stockpiles available which were found as coalition forces advanced north.
- 1988: Over the span of two days in March, the ethnic Kurd city of Halabja in northern Iraq (population 70,000) was bombarded with twenty chemical and cluster bombs, which included sarin. An estimated 5,000 people died.
- 1991: UN Resolution 687 establishes the term "weapon of mass destruction" and calls for the immediate destruction of chemical weapons in Iraq, and eventual destruction of all chemical weapons globally.
- 1993: The United Nations Chemical Weapons Convention is signed by 162 member countries, banning the production and stockpiling of many chemical weapons, including sarin. It goes into effect on 29 April 1997, and calls for the

complete destruction of all specified stockpiles of chemical weapons by April 2007.

- 1994: The Japanese religious sect Aum Shinrikyo releases an impure form of sarin in Matsumoto, Nagano Prefecture.
- 1995: Aum Shinrikyo sect releases an impure form of sarin in the Tokyo subway.
- 1998: In its June 15 issue Time Magazine runs a story entitled "Did The U.S. Drop Nerve Gas?". The story is broadcast June 7 on the CNN program NewsStand. The Time article alleges that U.S. Air Force A-1E Skyraiders engaged in a covert operation called Operation Tailwind, in which they deliberately dropped CBU-15 Cluster Bomb Units containing submunitions that were filled with sarin on defected U.S. troops in Laos. The report causes a scandal, and The Pentagon launches a study that concludes no nerve gas use took place. After an internal investigation, CNN and Time magazine (both owned by the media conglomerate Time Warner) retract the story and fire the two producers primarily responsible for it.
- 2004: May 14 Iraqi insurgency fighters in Iraq detonate a 155 mm shell containing several litres of binary precursors for sarin. The shell is designed to mix the chemicals as it spins during flight. The detonated shell releases only a small amount of sarin gas, either because the explosion failed to mix the binary agents properly or because the chemicals inside the shell had degraded significantly with age. Two United States soldiers were treated for exposure after displaying the early symptoms.

- Stockholm International Peace Research Institute entry on sarin

References

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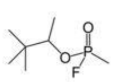
Soman



Discovered by Richard Kuhn

Discovered in 1944

Chemical characteristics

Chemical name

3-(fluoro-methyl-phosphoryl)oxy-
2,2-dimethyl-butane

Chemical family

Fluorinated organophosphorus compound

Chemical formula

$C_7H_{16}FO_2P$

Boiling point

198 °C

Freezing/melting point

42 °C (44 °F)

Vapor pressure

0.40 mmHg (53 Pa) at 25 °C

Vapor relative density (air=1)

6.3

Solubility in water

Moderate

Density at 25 C

1.022 g/cm^3

Appearance and color

When pure, colorless liquid with fruity odor.
With impurities, amber or dark brown,
with oil of camphor odor

Soman, also known by its NATO designation *GD* (O-Pinacolyl methylphosphonofluoridate) is an extremely toxic substance whose sole application is as

one of the world's most dangerous military weapons. It is a nerve agent, interfering with normal functioning of the mammalian nervous system. As a chemical weapon, it is classified as a weapon of mass destruction by the United Nations according to UN Resolution 687, and its production is strictly controlled and stockpiling outlawed by the Chemical Weapons Convention of 1993. Soman was the third of the so-called G-series nerve agents to be discovered (along with GA (tabun), GB (sarin), and GF (cyclosarin)).

It is a volatile, corrosive and colourless liquid with a faint odour when pure. More commonly, it is a yellow to brown color and has a stronger odour described as camphor. The LCt_{50} for Soman is 70 mg·min/m^3 in humans. It is both more lethal and more persistent than sarin or tabun, but less so than cyclosarin.

GD can be thickened for use as a chemical spray using an acryloid copolymer. It can also be deployed as a binary chemical weapon; its precursor chemicals are methylphosphonyl difluoride and a mixture of pinacolyl alcohol and an amine.

Alternative names

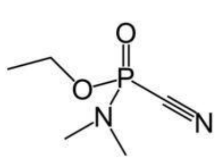
Soman is occasionally referred to names other than soman or GD:

- Phosphonofluoridic acid, methyl-, 1, 2, 2-trimethylpropyl ester
- Pinacolyl methylphosphonofluoridate
- 1,2,2-Trimethylpropyl methylphosphonofluoridate
- Methylpinacolyloxyfluorophosphine oxide
- Pinacolyloxymethylphosphonyl fluoride
- Pinacolyl methanefluorophosphonate
- Methylfluoropinacolylphosphonate
- Fluoromethylpinacolyloxyphosphine Oxide
- Methylpinacolyloxyphosphonyl fluoride
- Pinacolyl methylfluorophosphonate
- 1,2,2-Trimethylpropoxyfluoromethylphosphine oxide

History

Soman was discovered by Richard Kuhn in Germany in 1944, and represented the last wartime nerve agent discovery (GF was not found until 1949). Soman was given the identifier GD post-war (GC was already in medical use) when the information relating to soman was recovered by the Soviet Union from its hiding place in a mine.

Tabun



Discovered by Gerhard Schrader

Discovered in 1936

Chemical characteristics

Chemical name

Ethyl N,N-dimethylphosphoramidocyanidate

Chemical family

Organophosphorus compound

Chemical formula

$C_5H_{11}N_2O_2P$

NFPA Rating

- **Health - 4**
- **Flammability - 2**
- **Reactivity - 1**

Boiling point

247.5 °C (477.5 °F) / 907.17°R

Freezing/melting point

50 °C (58 °F) / 401.67°R

Vapor pressure

0.07 mmHg (9 Pa) at 25 °C

Vapor Density (Air=1)

5.6

Liquid density

1.0887 g/cm³ at 25 °C
1.102 g/cm³ at 20 °C

Solubility in water

9.8 g/100 g at 25 °C
7.2 g/100 g at 20 °C

Specific gravity

Not available

Appearance and color

Colorless to brown liquid.
Faintly fruity odor (none when pure)

Fire and Explosion Data

Flashpoint

78 °C (172 °F) / 631.67°R

Unusual hazards

Fires involving this chemical may result
in the formation of hydrogen cyanide

Tabun or *GA* (Ethyl N,N-dimethylphosphoramidocyanidate) is an extremely toxic substance that is one of the world's most dangerous military weapons. Because it fatally interferes with normal functioning of the mammalian nervous system, it is classified as a nerve agent. As a chemical weapon, it is classified as a weapon of mass destruction by the United Nations according to UN Resolution 687, and its production is strictly controlled and stockpiling outlawed by the Chemical Weapons Convention of 1993. Tabun is the first of the so-called G-series nerve agents (along with GB (sarin), GD (soman) and GF (cyclosarin)).

Tabun is a colourless to brown liquid (depending on purity). It is volatile (evaporating readily at normal temperatures), although less volatile than either sarin or soman.

Effects of overexposure

The exact symptoms of overexposure are similar to those created by all nerve agents, and are described in more detail in that article. Tabun, like all nerve agents, is toxic even in minute doses. The number and severity of symptoms which appear vary according to the amount of the agent absorbed and rate of entry into the body. Very small skin dosages

sometimes cause local sweating and tremors accompanied with characteristically constricted pupils with few other effects. Tabun is about half as toxic as sarin by inhalation, but tabun in very low concentrations is more irritating to the eyes than sarin.

The effects of exposure appear much more slowly when tabun is absorbed through the skin rather than inhaled: although a victim may absorb a lethal dose in 1 to 2 minutes, death may be delayed for 1 to 2 hours. Inhaled lethal dosages kill in 1 to 10 minutes, and liquid in the eye kills almost as rapidly. Most of what is known about lethal dosages are known from animal studies on monkeys.

Alternative names

Tabun is occasionally referred to names other than tabun or GA:

- Ethyl dimethylplosphoramidocyanidate
- Dimethylaminoethoxy-cyanophosphine oxide
- Dimethylamidoethoxyphosphoryl cyanide
- Ethyldimethylaminocyanophosphonate
- Ethyl ester of dimethylphosphoroamidocyanidic acid
- Ethyl phosphorodimethylamidocyanidate
- EA1205

History

For an in-depth discussion, see main article on nerve agent history

Tabun, the first known nerve agent, was discovered accidentally in 1936 by the German researcher Dr. Gerhard Schrader. Dr. Schrader was experimenting with a class of compounds called organophosphates, which kill insects by interrupting their nervous systems, in order to create a more effective insecticide for the IG Farben pharmaceutical conglomerate at Elberfield. Instead of a new insecticide, however, he discovered tabun, a chemical which is enormously toxic to humans as well as to insects.

During World War II as part of the Grün 3 program, a plant for the manufacture of tabun was established in Dyhernfurth (now Brzeg Dolny, Poland), producing the nerve agent under the codename Trilon-83. Run by Anorgana GmbH, the plant began production in 1942. Large scale manufacturing of the agent resulted in problems with the product's degradation over time and only around 12,500 tons of material were manufactured before the plant was over-run by the advancing Soviet forces. The plant initially produced shells and aerial bombs using a 95:5 mix of tabun and chlorobenzene, designated "Variant A" before switching in the latter half of the war to "Variant B," an 80:20 mix of tabun and chlorobenzene designed to make the mixture disperse more easily. The Soviet government had the plant dismantled and taken back to Russia.

Like the other Allied governments, the Soviets soon abandoned GA for GB and GD. Large quantities of the German-manufactured agent were dumped into the sea.

Since GA is much easier to produce than the other G-series weapons and the process is comparatively widely understood, countries which are developing a nerve agent capability but which lack advanced industrial facilities often start by producing GA.

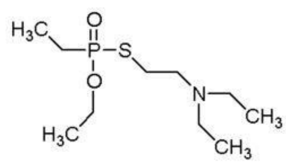
During the Iran-Iraq War, Iraq employed large quantities of chemical weapons against ground forces of Iran. Although the most commonly used agents were mustard gas and sarin, tabun and cyclosarin were also used.

See also

- nerve agent

VE

VE (nerve agent)



Systematic name S-(Diethylamino)ethyl O-ethyl ethylphosphonothioate

Chemical formula $C_{10}H_{24}N_{1}O_{2}P_{1}S_{1}$

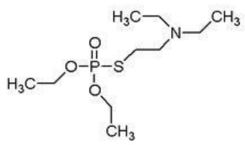
Molecular mass 253.34 g/mol

VE (S-(Diethylamino)ethyl O-ethyl ethylphosphonothioate) is a "V-series" nerve agent closely related to the better-known VX nerve agent.

Like most of the agents in the V-series (with the exception of VX), VE has not been extensively studied outside of military science. Little is known about this compound other than its chemical formula.

It is commonly theorized that the so called "second-generation" V series agents came from a cold war era Russian chemical weapons development program. They may have been developed sometime between 1950 and 1990. They have similar lethal dose levels to VX (between 10-50 mg) and have similar symptoms and method of action to other nerve agents that act on cholinesterase, and treatment remains the same, but the window for effectively treating second generation V series seizures is shorter. In addition to the standard seizures, some of the second generation V series agents are known to cause comas.

VG



VG (O,O-Diethyl-S-[2-(diethylamino)ethyl] phosphorothioate) (also called *Amiton* or *Tetram*) is a "V-series" nerve agent chemically similar to the better-known VX nerve agent. Tetram is the common Russian name for the substance. Amiton was the trade name for the substance when it was marketed as an insecticide by ICI in the mid-1950s.

With a toxicity of about 1/10 that of VX, i.e. similar to that of sarin[1], it is now considered too dangerous for use in agriculture[2] but unlike other nerve agents it is classified under Schedule 2 of the Chemical Weapons Convention rather than the more restrictive Schedule 1. It is thought that North Korea may have military stockpiles of this chemical [3].

During the early 1950s at least three chemical companies working on organo-phosphorus insecticides independently discovered the amazing toxicity of these chemicals.[4] In 1952, Dr. Ranajit Ghosh, a chemist working for ICI at their Plant Protection Laboratories was investigating the potential of organophosphate esters of substituted aminoethanethiols for use as pesticides. Like the earlier German investigators of organophosphates in the late 1930s who had discovered the G-series nerve agents, Dr. Ghosh discovered that their action on cholinesterase made them effective pesticides. One of them, Amiton, was described in a 1955 paper by Ghosh and another chemist, J. F. Newman, as being particularly effective against mites[5]. It was brought to market as an insecticide by the company in 1954 but was subsequently withdrawn as too toxic. [6]

The toxicity of these substances had not passed unnoticed by the British Government, as some of the compounds had already been sent to their research facility at Porton Down for evaluation. Some of the chemicals from this class of compounds formed a new group of nerve agents called V Agents. The British Government unilaterally renounced chemical and biological weapons in 1956, although in 1958 traded their research on VX technology with the United States Government in exchange for information on thermonuclear weapons. The US then went into production of large amounts of the chemically similar, but much more toxic VX in 1961[7].

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2. ^ Theodore Karasik. Toxic Warfare. RAND. Retrieved on 2006-10-07.
3. ^ North Korea Profile Chemical Agents VG (Amiton, Tetram). *Nuclear Threat Initiative*. **Retrieved on 2006-10-07.**
4. ^ Nerve Agents - Lethal organo-phosphorus compounds inhibiting cholinesterase. *Organisation for the Prohibition of Chemical Weapons website*. **Retrieved on 2006-10-07.**

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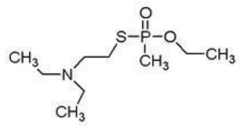
VM

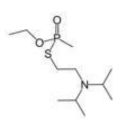


VM (Phosphonothioic acid, methyl-, S-(2-(diethylamino)ethyl) O-ethyl ester) is a "V-series" nerve agent closely related to the better-known VX nerve agent.

Like most of the agents in the V-series (with the exception of VX), VM has not been extensively studied outside of military science. Little is known about this chemical compound other than its chemical formula.

It is commonly theorized that the so called "second-generation" V series agents came from a cold war era Russian chemical weapons development program. They may have been developed sometime between 1950 and 1990. They have similar lethal dose levels to VX (between 10-50 mg) and have similar symptoms and method of action to other nerve agents that act on cholinesterase. The treatment remains the same, but the window for effectively treating second generation V series seizures is shorter. In addition to the standard seizures, some of the second generation V series agents are known to cause comas.

VX



Discovered by Ranajit Ghosh

Discovered in 1952

Chemical characteristics

Chemical name

O-ethyl S-(2-diisopropylaminoethyl)

methylphosphonothioate

Chemical family

Organophosphorus compound

Chemical formula

$C_{11}H_{26}NO_2PS$

NFPA Rating

- **Health - 4**
- **Flammability - 1**
- **Reactivity - 0**

Boiling point

298°C (568.4°F)

Freezing/melting point

50°C (58°F)

Vapor pressure

0.007 mmHg (? Pa) at 25 °C

Vapor Density (Air=1)

9.2

Liquid density

1.0083 g cm³

Specific gravity

1.0113

Appearance and color

Colorless

The *VX* nerve agent is the most well-known of the V-series of nerve agents. Its chemical name is O-ethyl-S-[2(diisopropylamino)ethyl] methylphosphonothioate and its molecular formula is $C_{11}H_{26}NO_2PS$.

The only countries known to possess VX are the United States, United Kingdom, Russia, France and Syria. VX agent is considered an area denial weapon due to its physical properties.

With its high viscosity and low volatility VX has the texture and feel of high-grade motor oil. This makes it especially dangerous, as it has a high persistence in the environment. It is odorless and tasteless, and can be distributed as a liquid or, through evaporation, into small amounts of vapor. It works as a nerve agent by blocking the function of the enzyme acetylcholinesterase. Normally, an electric nerve pulse would cause the release of acetylcholine over a synapse that would stimulate muscle contraction. The acetylcholine is then broken down to non-reactive substances (acetic acid and choline) by the acetylcholinesterase enzyme. If more muscle tension is needed the nerve must release more acetylcholine. VX blocks the action of acetylcholinesterase, thus resulting in sustained contractions of all the muscles in the body. Sustained contraction of the diaphragm muscle causes death by asphyxiation.

Often regarded as the deadliest nerve agent created to date, as little as 200 micrograms is enough to kill an average person, depending on method of absorption. Death can be avoided if the appropriate antidote is injected immediately after exposure. The most commonly used antidote is atropine and pralidoxime which is issued for military personnel in the form of an autoinjector. Standard chemical agent resistance pills are also effective. Atropine works by binding and blocking a subset of acetylcholine receptors (known as muscarinic acetylcholine receptor, mAchR), so that the build up of acetylcholine produced by loss of the acetylcholinesterase function can no longer affect their target. This prevents involuntary muscle actions so that muscles like the diaphragm are not in constant contraction. The injection of pralidoxime regenerates bound acetylcholinesterase.

Synthesis

VX is produced via the "Transester Process". This entails a complex chemical transition whereby phosphorus trichloride is methylated to produce methyl phosphonous dichloride. The resulting material is reacted with ethanol to form a diester. This is then transesterified to produce the immediate precursor of VX. Finally, the immediate precursor is reacted with sulfur to form V-agent.

Nerve Agent VX can also be delivered in binary chemical weapons which mix in-flight to form the agent prior to release. Binary VX is referred to as VX2, and is created by mixing O-(2-diisopropylaminoethyl) O'-ethyl methylphosphonite (Agent QL) with elemental sulfur (Agent NE) as is done in the BIGEye aerial chemical bomb. It may also be produced by mixing with sulfur compounds, as with the liquid dimethyl polysulfide mixture (Agent NM) in the cancelled XM-768 8-inch binary projectile program.

History

The chemist Ranajit Ghosh discovered the V-series nerve agents at the Government research establishment at Porton Down, England in 1952; VX was passed over in favour of continuing with sarin as their chemical weapon of choice. The United Kingdom unilaterally renounced chemical and biological weapons in 1956. In 1958 the British government traded their research on VX technology with the United States of America in exchange for information on thermonuclear weapons. The US then went into production of large amounts of VX in 1961.

The US later destroyed all of its stockpiles of the deadly nerve agent (by incineration at Johnston Island in the South Pacific), as mandated by the US accession to the Chemical Weapons Convention. Earlier, pre-treaty disposal included the US Army's CHASE (Cut Holes And Sink 'Em) program, in which old ships were filled with chemical weapons stockpiles and then scuttled. CHASE 8 was conducted on June 15, 1967, in which the S.S. Cpl. Eric G. Gibson was filled with 7,380 VX rockets and scuttled in 7,200 feet of water, off the coast of Atlantic City, New Jersey. The long-term environmental ramifications of exposing large quantities of VX to seawater and marine life could pose a grave danger, but are ultimately unknown.

The US is also destroying chemical weapons stockpiles containing VX in nine other locations, one of which is in Russia. On June 12, 2005, it was reported that more than 250,000 US gallons (950 m^3) of the chemical weapon are stored at the Newport Chemical Depot in Newport, Indiana, about 30 miles (50 km) north of Terre Haute, Indiana. The VX is in the process of being hydrolyzed to much less toxic byproducts using concentrated caustic solution. The VX hydrolysate produced will contain mainly a phosphonate ester and a thiolamine, with 20 parts per billion or less of residual VX. (Interestingly, 20 ppb is the level of VX in water that is considered permissible for drinking by US combat troops.) The current plan is to truck the hydrolysate from Indiana to the DuPont Chambers Works Secure Environmental Facility at Deepwater, NJ where it will be further treated to destroy the phosphonate ester and the thiolamine, and dumped into the Delaware River.[1] The US Army is awaiting final approval of the plan from the Centers for Disease Control and the Environmental Protection Agency. The governors of Delaware, New Jersey, Pennsylvania, and New York have opposed this plan and the New Jersey Governor Codey instructed the New Jersey Department of Transportation to deny entry to any trucks carrying the hydrolysate to the Deepwater facility. Prior to the current plan, it had been proposed that the hydrolysate be dumped into the Great Miami River, a tributary of the Ohio River, near Dayton, Ohio but the community there successfully defeated the proposal.

VX hydrolysis began on May 5 2005 and as of June 12 the facility had destroyed 2,894 US gallons (11 m^3) of VX. A contained spill of 30 US gallons (100 L) drew attention to the disposal process, but authorities said no agent was released and no one was injured in the spill.

VX was synthesised and used for several murders and attempted murders by the Aum Shinrikyo cult in Japan in 1994 and 1995.[2]

References

1. ^ Montgomery, Jeff. "Army backs VX disposal at N.J. facility", The News Journal, 2006-04-26, p. A2.

2. ^ Chronology of Aum Shinrikyo's CBW Activities **(pdf).**

See also

- Nerve Agents In Fiction
-

Choline esters - Acetylcholine

Identifiers

CAS number 51-84-3

ATC code S01**EB09**

PubChem 187

DrugBank EXPT00412

Chemical data

Formula C***7***H***16***N***1***O***2***+

Mol. weight 450.197 g/mol

SMILES CC(OCC[N](C)(C)C)=O

The chemical compound *acetylcholine*, often abbreviated as *ACh*, was the first neurotransmitter to be identified. It is a chemical transmitter in both the peripheral nervous system (PNS) and central nervous system (CNS) in many organisms including humans. Acetylcholine is the neurotransmitter in all autonomic ganglia.

Chemistry

Acetylcholine is an ester of acetic acid and choline with chemical formula CH3COOCH2CH2N+(CH3)3. This structure is reflected in the systematic name, 2-(acetyloxy)-N,N,N-trimethylethanaminium.

Acetylcholine (ACh) was first identified in 1914 by Henry Hallett Dale for its actions on heart tissue. It was confirmed as a neurotransmitter by Otto Loewi who initially gave it the name vagusstoff because it was released from the vagus nerve. Both received the 1936 Nobel Prize in Physiology or Medicine for their work.

Later work showed that when acetylcholine binds to acetylcholine receptors on striated muscle fibers, it opens voltage gated sodium channels in the membrane. Sodium ions then enter the muscle cell, stimulating muscle contraction. Acetylcholine is also used in the brain, where it tends to cause excitatory actions. The glands that receive impulses from the parasympathetic part of the autonomic nervous system are also stimulated in the same way.

Acetylcholine is synthesized in certain neurons by the enzyme choline acetyltransferase from the compounds choline and acetyl-CoA. Organic mercurial compounds have a high affinity for sulfhydryl groups, which causes dysfunction of the enzyme choline acetyl transferase. This inhibition may lead to acetylcholine deficiency, and can have consequences on motor function.

Normally, the enzyme acetylcholinesterase converts acetylcholine into the inactive metabolites choline and acetate. The devastating effects of nerve agents (in bioterrorism, Sarin gas for example) are due to their inhibition of this enzyme, resulting in continuous stimulation of the muscles, glands and central nervous system. Certain insecticides are effective because they inhibit this enzyme in insects. On the other hand, since a shortage of acetylcholine in the brain has been associated with Alzheimer's disease, some drugs that inhibit acetylcholinesterase are used in the treatment of that disease.

Release sites

- Acetylcholine is released in the autonomic nervous system:
  - pre- and post-ganglionic parasympathetic neurons
  - preganglionic sympathetic neurons (and also postganglionic sudomotor neurons, i.e., the ones that control sweating)

Botulin acts by suppressing the release of acetylcholine; where the venom from a black widow spider has the reverse effect.

Pharmacology

There are two main classes of acetylcholine receptor (AChR), nicotinic acetylcholine receptors (nAChR) and muscarinic acetylcholine receptors (mAChR). They are named for the ligands used to discover the receptors.

Nicotinic AChRs are ionotropic receptors permeable to sodium, potassium, and chloride ions. They are stimulated by nicotine and acetylcholine and blocked by curare. Most peripheral AChRs are nicotinic, such as those on the heart and blood vessels or at the neuromuscular junction. They are also found in wide distribution through the brain, but in relatively low numbers.

Muscarinic receptors are metabotropic and affect neurons over a longer time frame. They are stimulated by muscarine and acetylcholine, and blocked by atropine. Muscarinic receptors are found in both the central nervous system and the peripheral nervous system, in heart, lungs, upper GI tract and sweat glands. Extracts from the plant included this compound, and its action on muscarinic AChRs that increased pupil size was used for attractiveness in many European cultures in the past. Now, ACh is sometimes used during cataract surgery to produce rapid constriction of the pupil. It must be administered intraocularly because corneal cholinesterase metabolizes topically administered ACh before it can diffuse into the eye. It is sold by the trade name Miochol-E (CIBA Vision). Similar drugs are used to induce mydriasis (dilation of the pupil) in cardiopulmonary resuscitation and many other situations.

The disease myasthenia gravis, characterized by muscle weakness and fatigue, occurs when the body inappropriately produces antibodies against acetylcholine receptors, and thus inhibits proper acetylcholine signal transmission. Over time the motor end plate is destroyed. Drugs that competitively inhibit acetylcholinesterase (e.g., neostigmine or physostigmine) are effective in treating this disorder. They allow endogenously released acetylcholine more time to interact with its respective receptor before being inactivated by acetylcholinesterase in the gap junction.

Blocking, hindering or mimicking the action of acetylcholine has many uses in medicine. Cholinesterase inhibitors increase the action of acetylcholine by delaying its degradation; some have been used as nerve agents or pesticides. Clinically they are used to reverse the action of muscle relaxants, to treat myasthenia gravis and in Alzheimer's disease (rivastigmine, which increases cholinergic activity in the brain).

ACh Receptor Agonists

Direct Acting

- Acetylcholine
Bethanechol
Carbachol
Cevimeline
Pilocarpine
Suberylcholine

Indirect Acting (reversible)

- Ambenomium
- Donepezil
- Edrophonium
- Galantamine
- Neostigmine
- Physostigmine
- Pyridostigmine
- Rivastigmine
- Tacrine

Indirect Acting (irreversible)

- Echothiophate
- Isoflurophate

Reactivation of Acetylcholine Esterase

- Pralidoxime

ACh Receptor Antagonists

Antimuscarinic Agents

- Atropine
    - Ipratopium
- Scopolamine

Ganglionic Blockers

- Mecamylamine
Hexamethonium
- Nicotine (in high doses)
- Trimethaphan

Neuromuscular Blockers

- Atracurium
Cisatracurium
- Doxacurium
- Metocurine
- Mivacurium
- Pancuronium
- Rocuronium
- Succinylcholine
- Tubovurarine
- Vecuronium

Others? / Uncategorized / Unknown

- surugatoxin

Neuromodulatory Effects

In the central nervous system, ACh has a variety of effects as a neuromodulator.

Given its prominent role in learning, ACh is naturally involved with synaptic plasticity. It has been shown to enhance the amplitude of synaptic potentials following long-term potentiation in many regions, including the dentate gyrus, CA1, piriform cortex, and neocortex. This effect most likely occurs either through enhancing currents through NMDA receptors or indirectly by suppressing adaptation. The suppression of adaptation has been shown in brain slices of regions CA1, cingulate cortex, and piriform cortex as well as in vivo

in cat somatosensory and motor cortex by decreasing the conductange of voltage-dependent M currents and Ca2+-dependent K+ currents.

Acetylcholine also has other effects on excitability of neurons. Its presence causes a slow depolarization by blocking a tonically active K+ current, which increases neuronal excitability. Paradoxically, it increases spiking activity in inhibitory interneurons while decreasing strength of synaptic transmission from those cells. This decrease in synaptic transmission also occurs selectively at some excitatory cells: for instance, it has an effect on intrinsic and associational fibers in layer Ib of piriform cortex, but has no effect on afferent fibers in layer Ia. Similar laminar selectivity has been shown in dentate gyrus and region CA1 of the hippocampus. One theory to explain this paradox interprets Acetylcholine neuromodulation in the neocortex as modulating the estimate of expected uncertainty, acting counter to Norepinephrine (NE) signals for unexpected uncertainty. Both would then decrease synaptic transition strength, but ACh would then be needed to counter the effects of NE in learning a signal understood to be noisy.

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Muscarinic agonists

A *muscarinic receptor agonist* is an agent that enhances the activity of the muscarinic acetylcholine receptor. The muscarinic receptor has different subtypes, labelled M1-M5, allowing for further differentiation.

In the form of pilocarpine muscarinic receptor agonists have been used medically for a long time.

M1-type muscarinic acetylcholine receptors play a role in cognitive processing. In Alzheimer disease (AD) amyloid formation may decrease the ability of these receptors to transmit their signals leading to decrease cholinergic activity. As these receptors themselves

appear relatively unchanged in the disease process, they have become a potential therapeutic target when trying to improve cognitive function in patients with AD.

A number of muscarinic agonists have been developed and are under investigation to treat AD. These agents show promise as they are neurotrophic, decrease amyloid depositions, and improve damage due to oxidative stress. Tau-phosphorylation is decreased and cholinergic function enhanced. Notably several agents of the AF series of muscarinic agonists have become the focus of such research:. *AF102B, AF150(S), AF267B*. In animal models that are mimicking the damage of AD, these agents appear promising.

Drugs

- M1 agonists
  - *Cevimeline* (AF102B) (Evoxac?) is a muscarinic agonist that is an Food and Drug Administration (FDA)-approved drug and used for the management of dry mouth in Sjogren syndrome.
- M3 agonists
  - *Aceclidine*, for glaucoma.
  - *Arecoline*, an alkaloid present in the Betel nut.
  - *Pilocarpine* is a drug that acts as a muscarinic receptor agonist that is used to treat glaucoma.

See also

- Muscarine

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Muscarine

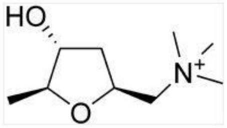
Chemical name (2S,4R,5S)-(4-hydroxy-5-methyl-tetrahydrofuran- 2-ylmethyl)-trimethyl-ammonium

Chemical formula $C_9H_{20}NO_2^+$

Molecular mass 174.26 g/mol

CAS number 300-54-9

SMILES *O[C@@H]1C[C@@H](C[N+](C)(C)C)O[C@H]1C*



Muscarine, L-*(+)-muscarine*, or *muscarin* is a natural product found in certain mushrooms, particularly in Inocybe and Clitocybe species. It was first isolated from Amanita muscaria in 1869. It was the first parasympathomimetic substance ever studied and causes profound activation of the peripheral parasympathetic nervous system that may end in convulsions and death. Muscarine has no effects on the central nervous system because it does not cross the blood-brain barrier due to its positively charged nitrogen atom.

Muscarine mimics the action of the neurotransmitter acetylcholine at metabotropic receptors that are also known under the name muscarinic acetylcholine receptors.

Muscarine poisoning is characterized by increased salivation, sweating (perspiration), and tearflow (lacrimation) within 15 to 30 minutes after ingestion of the mushroom. With large doses, these symptoms may be followed by abdominal pain, severe nausea, diarrhea, blurred vision, and labored breathing. Intoxication generally subsides within 2 hours. Deaths are rare, but may result from cardiac or respiratory failure in severe cases. The specific antidote is atropine.

Muscarine is only a trace compound in the fly agaric Amanita muscaria, the pharmacologically more relevant compound from this mushroom is muscimol.

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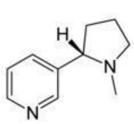
Nicotinic agonists

Nicotine



Chemical name (S)-3-(1-Methyl-2-pyrroli- dinyl)pyridine

Chemical formula $C_{10}H_{14}N_2$

Molecular mass 162.23 g/mol

CAS number 54-11-5

SMILES *[H][C@@]2(N(C)CCC2)c1cccnc1*

Properties

Density 1.01 g/ml

Melting point -79 °C

Boiling point 247 °C (decomposes)

Autoignition temperature 240 °C

Flash point 95 °C

Vapour Pressure 0.006 kPa at 25 °C

Viscosity 2.7 mPa·s at 25 °C, 1.6 mPa·s at 50 °C

Surface Tension 37.5 dyn/cm (37.5 mN/m) at 25.5 °C, 37.0 dyn/cm (37.0 mN/m) at 36.0 °C

Except where noted otherwise, data are given for materials in their standard state (at 25 °C, 100 kPa)

Nicotine is an alkaloid found in the nightshade family of plants (Solanaceae), predominantly in tobacco, and in lower quantities in tomato, potato, eggplant (aubergine), and green pepper. Nicotine alkaloids are also found in the leaves of the coca plant. Nicotine constitutes 0.3 to 5% of the tobacco plant by dry weight, with biosynthesis taking place in the roots, and accumulates in the leaves. It is a potent neurotoxin and is included in many insecticides.

In lower concentrations, the substance acts as a stimulant and is one of the main factors responsible for the dependence-forming properties of tobacco smoking.

Chemistry

Nicotine is a hygroscopic, oily liquid that is miscible with water in its base form. As a nitrogenous base, nicotine forms salts with acids that are usually solid and water soluble. Nicotine easily penetrates the skin. As shown by the physical data, free base nicotine will burn at a temperature below its boiling point, and its vapors will combust at 95 °C in air despite a low vapor pressure. Because of this, most nicotine is burned when a cigarette is smoked; however, enough is inhaled to provide the desired effects.

Pharmacology

Pharmacokinetics: As nicotine enters the body, it is distributed quickly through the bloodstream and can cross the blood-brain barrier. On average it takes about seven seconds for the substance to reach the brain. The half life of nicotine in the body is around 2 hours[1]. The amount of nicotine inhaled with tobacco smoke is a fraction of the amount contained in the tobacco leaves (most of the substance is destroyed by the heat). The amount of nicotine absorbed by the body from smoking depends on many factors, including the type of tobacco, whether the smoke is inhaled, and whether a filter is used. For chewing tobacco, often called dip, snuff, or snus, which is held in the mouth between the lip and gum, the amount released into the body tends to be much greater than smoked tobacco.

Dynamics

Nicotine acts on the nicotinic acetylcholine receptors. In small concentrations it increases the activity of these receptors, among other things leading to an increased flow of adrenaline, a stimulating hormone. The release of adrenaline causes an increase in heart rate, blood pressure and respiration, as well as higher glucose levels in the blood. Cotinine is a break-down product of nicotine which remains in the blood for up to 48 hours and can be used as an indicator of a person's exposure to smoke. In high doses, nicotine will cause a blocking of the nicotinic acetylcholine receptor, which is the reason for its toxicity and its effectiveness as an insecticide.

In addition, nicotine increases dopamine levels in the reward circuits of the brain. Studies have shown that smoking tobacco inhibits monoamine oxidase (MAO), an enzyme responsible for breaking down monoaminergic neurotransmitters such as dopamine, in the brain. It is currently believed that nicotine by itself does not inhibit the production of monoamine oxidase (MAO), but that other ingredients in inhaled tobacco smoke are believed to be responsible for this activity. In this way, it generates feelings of pleasure, similar to that caused by cocaine and heroin, thus causing the addiction associated with the need to sustain high dopamine levels.

Toxicology

The LD50 of nicotine is 50 mg/kg for rats and 3 mg/kg for mice. 40–60 mg can be a lethal dosage for adult human beings. This makes it an extremely deadly poison. It is more toxic than many other alkaloids such as cocaine, which has a lethal dose of 1000 mg.

The carcinogenic properties of nicotine in standalone form, separate from tobacco smoke, have not been evaluated by the IARC, and it has not been assigned to an official carcinogen group. The currently available literature indicates that nicotine, on its own, does not promote the development of cancer in healthy tissue and has no mutagenic properties. Its teratogenic properties have not yet been adequately researched, and while the likelihood of birth defects caused by nicotine is believed to be very small or nonexistent, nicotine replacement product manufacturers recommend consultation with a physician before using a nicotine patch or nicotine gum while pregnant or nursing. However, nicotine and the increased acetylcholinic activity it causes have been shown to impede apoptosis, which is one of the methods by which the body destroys unwanted cells (programmed cell death). Since apoptosis helps to remove mutated or damaged cells that may eventually become cancerous, the inhibitory actions of nicotine creates a more favourable environment for cancer to develop. Thus nicotine plays an indirect role in carcinogenesis. It is also important to note that its addictive properties are often the primary motivating factor for tobacco smoking, contributing to the proliferation of cancer.

At least one study has concluded that exposure to nicotine alone, not simply as a component of cigarette smoke, could be responsible for some of the neuropathological changes observed in infants dying from Sudden Infant Death Syndrome (SIDS).[2]

It has been noted that the majority of people diagnosed with schizophrenia smoke tobacco. Estimates for the number of schizophrenics that smoke range from 75% to 90%. It

was recently argued that the increased level of smoking in schizophrenia may be due to a desire to self-medicate with nicotine. [3][4] More recent research has found the reverse, that it is a risk factor without long-term benefit, used only for its short term effects. [5]However, research on nicotine as administered through a patch or gum is ongoing.

Therapeutic uses

The primary therapeutic use of nicotine is in treating nicotine dependence (smoking). Controlled levels of nicotine are given to a patient through gums, dermal patches, or nasal sprays in an effort to wean them off of their dependence.

Recent studies have indicated that nicotine can be used to help adults suffering from autosomal dominant frontal lobe epilepsy. The same areas that cause seizures in that form of epilepsy are also responsible for processing nicotine in the brain.

Some research has also shown that nicotine can lessen symptoms of mild to moderate ulcerative colitis.

Nicotine and its metabolites are being researched for the treatment of a number of disorders, including ADHD and Parkinson's Disease.

History and name

Nicotine is named after the tobacco plant Nicotiana tabacum, which in turn is named after Jean Nicot, a French ambassador, who sent tobacco and seeds from Portugal to Paris in 1550 and promoted their medicinal use. Nicotine was first isolated from the tobacco plant in 1828 by German chemists, Posselt & Reimann. Its chemical empirical formula was described by Melsens in 1843, and it was first synthesized by A. Pictet and Crepieux in 1893.

See also

- Psychoactive drug

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2. ^ Machaalani et al. (2005) "Effects of postnatal nicotine exposure on apoptotic markers in the developing piglet brain"
3. ^ Schizophr. Res. 2002
4. ^ Am. J. Psychiatry 1995
5. ^ Br. J. Psychiatry 2005

Pharmacology

Pharmacology (in Greek: pharmacon (Æ¬Á¼±º¿½) meaning drug, and logos (»Ì³¿Â) meaning science) is the study of how substances interact with living organisms to produce a change in function.[1] If substances have medicinal properties, they are considered *pharmaceuticals*. The field encompasses drug composition and properties, interactions, toxicology, therapy, and medical applications and antipathogenic capabilities.

Development of medication is a vital concern to medicine, but also has strong economical and political implications. To protect the consumer and prevent abuse, many governments regulate the manufacture, sale, and administration of medication. In the United States, the main body that regulates pharmaceuticals is the Food and Drug Administration and they enforce standards set by the United States Pharmacopoeia.

Pharmacology as a chemical science is practiced by pharmacologists. Subdisciplines include clinical pharmacology (the medical field of medication effects on humans), neuro- and psychopharmacology (effects of medication on behavior and nervous system functioning), toxicology and theoretical pharmacology.

Pharmacology is not identical with pharmacy, though in common usage the two are at times confused.

Drug legislation and safety

In the United States, the Food and Drug Administration (FDA) is responsible for creating guidelines for the approval and use of drugs. The FDA requires that all approved drugs fulfill two requirements:

1. The drug must be found to be effective against the disease for which it is seeking approval.
2. The drug must meet safety criteria by being subject to extensive animal and controlled human testing.

Gaining FDA approval usually takes several years to attain. Testing done on animals must be extensive and must include several species to help in the evaluation of both the effectiveness and toxicity of the drug. The dosage of any drug approved for use is intended to fall within a range in which the drug produces a theraputic effect or desired outcome.[1]

The safety and effectiveness of prescription drugs in the U.S. is regulated by the federal Prescription Drug Marketing Act of 1987.

Scientific background

The study of chemicals requires intimate knowledge of the biological system affected. With the knowledge of cell biology and biochemistry increasing, the field of pharmacology has also changed substantially. It has become possible, through molecular analysis of receptors, to design chemicals that act on specific cellular signalling or metabolic pathways by affecting sites directly on cell-surface receptors (which modulate and mediate cellular signalling pathways controlling cellular function).

A chemical has, from the pharmacological point-of-view, various properties. Pharmacokinetics describes the effect of the body on the chemical (e.g. half-life and volume of distribution), and pharmacodynamics describes the chemical's effect on the body (desired or toxic).

When describing the pharmacokinetic properties of a chemical, pharmacologists are often interested in ADME:

- Absorption - How is the medication absorbed (through the skin, the intestine, the oral mucosa)?
- Distribution - How does it spread through the organism?
- Metabolism - Is the medication converted chemically inside the body, and into which substances. Are these active? Could they be toxic?
- Excretion - How is the medication eliminated (through the bile, urine, breath, skin)?

Medication is said to have a narrow or wide therapeutic index or therapeutic window. This describes the ratio of desired effect to toxic effect. A compound with a narrow therapeutic index (close to one) exerts its desired effect at a dose close to its toxic dose. A compound with a wide therapeutic index (greater than five) exerts its desired effect at a dose substantially below its toxic dose. Those with a narrow margin are more difficult to dose and administer, and may require therapeutic drug monitoring (examples are warfarin, some antiepileptics, aminoglycoside antibiotics). Most anti-cancer drugs have a narrow therapeutic margin: toxic side-effects are almost always encountered at doses used to kill tumours.

Drugs used as medicines

Main article: Medication

A *medication* is a licensed drug (chemical) taken to cure or reduce symptoms of an illness or medical condition. Medications are generally divided into two groups -- over-the-counter (OTC) medications, which are available without special restrictions, and Prescription only medicines (POM), which must be prescribed by a physician. Most OTC medication is generally considered to be safe enough that most persons will not hurt themselves accidentally by taking it as instructed. Many countries, such as the UK have a third category of pharmacy medicines which can only be sold in registered pharmacies, by or under the supervision of a pharmacist. However, the precise distinction between OTC and prescription depends on the legal jurisdiction. Medications are typically produced by pharmaceutical companies and are often patented. Those that are not patented are called generic drugs.

Education

The study of pharmacology is typically offered as an advanced degree program.

In the United States, a few institutions have it available as an undergraduate major or concentration that enables graduates to be entry-level lab technicians in the field of drug design and discovery. The following universities offer the undergraduate major:

- Brody School of Medicine at East Carolina University - ECU Pharmacology Department

Duke University - Chemistry degree with Pharmacology concentration
Massachusetts College of Pharmacy and Health Sciences - School of Pharmacy
Purdue University - Bachelor of Science in Pharmaceutical Sciences
University at Buffalo, The State University of New York - Pharmaceutical Sciences Program
State University of New York at Stony Brook - Pharmacological Sciences
University of California, Santa Barbara - Pharmacology major
University of Michigan - B.S. in Pharmaceutical Sciences
University of the Sciences in Philadelphia - Pharmacology and Toxicology Program
University of Wisconsin-Madison - Pharmacology/Toxicology program (PDF)
University of Toledo - B.S. in Pharmaceutical Sciences

Also there is one high school in the United States that offers the Pharmacology course:

- Central High School (Philadelphia) -Pharmacology

See also

- Drug design
- Medicinal chemistry
- Pharmaceutical company
  - Prescription Drug Marketing Act (PDMA)
  - Psychopharmacology - medication for mental conditions

Footnotes

1. ^ a b Nagle, Hinter, Barbara Nagle (2005). Pharmacology: An Introduction. Boston: McGraw Hill. ISBN 0-07-312275-0.

Anatomical Therapeutic Chemical Classification System

The *Anatomical Therapeutic Chemical Classification System* is used for the classification of drugs. It is controlled by the WHO Collaborating Centre for Drug Statistics Methodology, and was first published in 1976.

Drugs are divided into different groups according to the organ or system on which they act and/or their therapeutic and chemical characteristics.

Classification

In the system drugs are classified into groups at 5 different levels:

First level

The first level of the code is based on a letter for the anatomical group and consists of one letter; there are 14 main groups:

A Alimentary tract and metabolism

B Blood and blood forming organs

C Cardiovascular system

D Dermatologicals

G Genito-urinary system and sex hormones

H Systemic hormonal preparations, excluding sex hormones and insulins

J Anti-infectives for systemic use

L Antineoplastic and immunomodulating agents

M Musculo-skeletal system

N Nervous system

P Antiparasitic products, insecticides and repellents

Q Veterinary drug

R Respiratory system

S Sensory organs

V Various

Second level

The second level of the code is based on the therapeutic main group and consists of two digits.

Third level

The third level of the code is based on the therapeutic/pharmacological subgroup and consists of one letter.

Fourth level

The fourth level of the code is based on the chemical/therapeutic/pharmacological subgroup and consists of one letter.

Fifth level

The fifth level of the code is based on the chemical substance subgroup and consists of two digits.

Further notes

The actual drug name used is the International Nonproprietary Name (INN) when available.

The ATC/DDD system is the ATC system with the addition of a measure of the assumed average maintenance dose per day for a drug used for its main indication in adults (Defined Daily Doses).

Other ATC classifications are ATCvet (for veterinary medicinal products) and ATC herbal classification (for herbal remedies).

The ATC classification system was based on the Anatomical Classification (AC-system) developed by the European Pharmaceutical Market Research Association (EPhMRA) and the Pharmaceutical Business Intelligence and Research Group (PBIRG).

Biotechnology

Biotechnology is technology based on biology, especially when used in agriculture, food science, and medicine. The UN Convention on Biological Diversity has come up with one of many definitions of biotechnology:[1]

"Biotechnology means any technological application that uses biological systems, living organisms, or derivatives thereof, to make or modify products or processes for specific use."

This definition is at odds with common usage in the United States, where "biotechnology" generally refers to recombinant DNA based and/or tissue culture based processes that have only been commercialized since the 1970s. Thus, in common usage, modifying plants or animals by breeding, which has been practiced for thousands of years, would not be considered biotechnology. This distinction emphasizes that modern, recombinant DNA based biotechnology is not just a more powerful version of existing technology, but represents something new and different; for instance, theoretically, recombinant DNA biotechnology allows us to take virtually any gene and express it in any organism; we can take the genes that make crimson color in plants and put them into guinea pigs to make pink pets, or, we can take the genes that help arctic fish survive the freezing temperatures and put

them into food to increase the amount of time it can grow before it freezes. This sort of gene transfer was virtually impossible with historical processes.

There has been a great deal of talk - and money - poured into biotechnology with the hope that miracle drugs will appear. While there do seem to be a small number of efficacious drugs, in general the Biotech revolution has not happened in the pharmaceutical sector. However, recent progress with monoclonal antibody based drugs, such as Genentech's Avastin (tm) suggest that biotech may finally have found a role in pharmaceutical sales.

Biotechnology can also be defined as the manipulation of organisms to do practical things and to provide useful products.

One aspect of biotechnology is the directed use of organisms for the manufacture of organic products (examples include beer and milk products). For another example, naturally present bacteria are utilized by the mining industry in bioleaching. Biotechnology is also used to recycle, treat waste, clean up sites contaminated by industrial activities (bioremediation), and produce biological weapons.

There are also applications of biotechnology that do not use living organisms. Examples are DNA microarrays used in genetics and radioactive tracers used in medicine.

Red biotechnology is applied to medical processes. Some examples are the designing of organisms to produce antibiotics, and the engineering of genetic cures through genomic manipulation.

White biotechnology, also known as *grey biotechnology*, is biotechnology applied to industrial processes. An example is the designing of an organism to produce a useful chemical. White biotechnology tends to consume less in resources than traditional processes used to produce industrial goods.

Green biotechnology is biotechnology applied to agricultural processes. An example is the designing of transgenic plants to grow under specific environmental conditions or in the presence (or absence) of certain agricultural chemicals. One hope is that green biotechnology might produce more environmentally friendly solutions than traditional industrial agriculture. An example of this is the engineering of a plant to express a pesticide, thereby eliminating the need for external application of pesticides. An example of this would be Bt corn. Whether or not green biotechnology products such as this are ultimately more environmentally friendly is a topic of considerable debate.

Bioinformatics is an interdisciplinary field which addresses biological problems using computational techniques. The field is also often referred to as computational biology. It plays a key role in various areas, such as functional genomics, structural genomics, and proteomics, and forms a key component in the biotechnology and pharmaceutical sector.

The term *blue biotechnology* has also been used to describe the marine and aquatic applications of biotechnology, but its use is relatively rare.

Biotechnology medical products

Traditional pharmaceutical drugs are small chemicals molecules that treat the symptoms of a disease or illness - one molecule directed at a single target. Biopharmaceuticals are large biological molecules known as proteins and these target the underlying mechanisms and pathways of a malady; it is a relatively young industry. They can deal with targets in humans

that are not accessible with traditional medicines. A patient typically is dosed with a small molecule via a tablet while a large molecule is typically injected.

Small molecules are manufactured by chemistry but large molecules are created by living cells: for example, - bacteria cells, yeast cell,animal cells.

Modern biotechnology is often associated with the use of genetically altered microorganisms such as E. coli or yeast for the production of substances like insulin or antibiotics. It can also refer to transgenic animals or transgenic plants, such as Bt corn. Genetically altered mammalian cells, such as Chinese Hamster Ovary (CHO) cells, are also widely used to manufacture pharmaceuticals. Another promising new biotechnology application is the development of plant-made pharmaceuticals.

Biotechnology is also commonly associated with landmark breakthroughs in new medical therapies to treat diabetes, hepatitis B, Hepatitis C, Cancers, Arthritis, Haemophilia Bone Fractures,Multiple Sclerosis, Cardiovascular as well as molecular diagnostic devices than can be used to define the patient population. Herceptin, is the first drug approved for use with a matching diagnostic test and is used to treat breast cancer in women whose cancer cells express the protein HER2.

History

Early cultures also understood the importance of using natural processes to breakdown waste products into inert forms. From very early nomadic tribes to pre-urban civilizations it was common knowledge that given enough time organic waste products would be absorbed and eventually integrated into the soil. It was not until the advent of modern microbiology and chemistry that this process was fully understood and attributed to bacteria.

The most practical use of biotechnology, which is still present today, is the cultivations of plants to produce food suitable to humans. Agriculture has been theorized to have become the dominant way of producing food since the Neolithic Revolution. The processes and methods of agriculture have been refined by other mechanical and biological sciences since its inception. Through early biotechnology farmers were able to select the best suited and high-yield crops to produce enough food to support a growing population. Other uses of biotechnology were required as crops and fields became increasingly large and difficult to maintain. Specific organisms and organism byproducts were used to fertilize, restore nitrogen, and control pests. Throughout the use of agriculture farmers have inadvertently altered the genetics of their crops through introducing them to new environments, breeding them with other plants, and by using artificial selection. In modern times some plants are genetically modified to produce specific nutritional values or to be economical.

The process of Ethanol fermentation was also one of the first forms of biotechnology. Cultures such as those in Mesopotamia, Egypt, and Iran developed the process of brewing which consisted of combining malted grains with specifics yeasts to produce alcoholic beverages. In this process the carbohydrates in the grains were broken down into alcohols such as ethanol. Later other cultures produced the process of Lactic acid fermentation which allowed the fermentation and preservation of other forms of food. Fermentation was also used in this time period to produce leavened bread. Although the process of fermentation was not fully understood until Louis Pasteur’s work in 1857, it is still the first use of biotechnology to convert a food source into another form.

Combinations of plants and other organisms were used as medications in many early civilizations. Since as early as 200 BC people began to use disabled or minute amounts of infectious agents to immunize themselves against infections. These and similar processes have been refined in modern medicine and have lead to many developments such as antibiotics, vaccines, and other methods of fighting sickness.

A more recent field in biotechnology is that of genetic engineering. Genetic modification has opened up many new fields of biotechnology and allowed the modification of plants, animals, and even humans on a molecular level.

Global biotechnology trends

According to Burrill and Company, an industry investment bank, over $350 billion has been invested in biotech so far, and global revenues have risen from $23 billion in 2000 to to more than $50 billion in 2005. The greatest growth has been in Latin America but all regions of the world have shown strong growth trends.

There has been little innovation in the traditional pharmaceutical industry over the past decade and biopharmaceuticals are now achieving the fastest rates of growth against this background, particularly in breast cancer treatment. Biopharmaceuticals typically treat sub-sets of the total population with a disease whereas traditional drugs are developed to treat the population as a whole. However, one of the great difficulties with traditional drugs are the toxic side effects the incidence of which can be unpredictable in individual patients.

Biotechnology firms

There are around 4,000 biotechnology firms across the globe. Almost 50% of these are in the European Union; 30% in the US and the balance in Asia. The leading biotechnology firms are Amgen, Genentech and Serono.

Key visionaries and personalities in biotechnology sector

- Finland : Leena Palotie
Iceland : Kari Stefansson
Ireland : Timothy O'Brien, Dermot P Kelleher, Pearse Lyons
USA : Kate Jacques, David Botstein, Craig Venter, Sydney Brenner, Eric Lander, Leroy Hood, Robert Langer, Henry I. Miller, Roger Beachy, William Rutter, George Rathmann, Herbert Boyer, Michael West, Thomas Okarma
Europe : Paul D Kemp
India : Kiran Mazumdar-Shaw (Biocon)
Canada : Mike Tyers

See also

- Pharmaceutical company

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1. ^ "The Convention on Biological Diversity (Article 2. Use of Terms)." United Nations. 1992. Retrieved on September 20, 2006.

Bioinformatics

Bioinformatics and *computational biology* involve the use of techniques including applied mathematics, informatics, statistics, computer science, artificial intelligence, chemistry and biochemistry to solve biological problems usually on the molecular level. Research in computational biology often overlaps with systems biology. Major research efforts in the field include sequence alignment, gene finding, genome assembly, protein structure alignment, protein structure prediction, prediction of gene expression and protein-protein interactions, and the modeling of evolution.

The terms bioinformatics and computational biology are often used interchangeably. However bioinformatics more properly refers to the creation and advancement of algorithms, computational and statistical techniques, and theory to solve formal and practical problems posed by or inspired from the management and analysis of biological data. Computational biology, on the other hand, refers to hypothesis-driven investigation of a specific biological problem using computers, carried out with experimental and simulated data, with the primary goal of discovery and the advancement of biological knowledge. A similar distinction is made by National Institutes of Health in their working definitions of Bioinformatics and Computational Biology, where it is further emphasized that there is a tight coupling of developments and knowledge between the more hypothesis-driven research in computational biology and technique-driven research in bioinformatics. Computational biology also includes lesser known but equally important subdisciplines such as computational biochemistry and computational biophysics.

A common thread in projects in bioinformatics and computational biology is the use of mathematical tools to extract useful information from data produced by high-throughput biological techniques such as genome sequencing. A representative problem in bioinformatics is the assembly of high-quality genome sequences from fragmentary "shotgun" DNA sequencing. Other common problems include the study of gene regulation using data from microarrays or mass spectrometry.

Major Research Areas

Sequence analysis

Since the Phage ¦-X174 was sequenced in 1977, the DNA sequences of hundreds of organisms have been decoded and stored in databases. These data are analyzed to determine genes that code for proteins, as well as regulatory sequences. A comparison of genes within a species or between different species can show similarities between protein functions, or relations between species (the use of molecular systematics to construct phylogenetic trees).

With the growing amount of data, it long ago became impractical to analyze DNA sequences manually. Today, computer programs are used to search the genome of thousands of organisms, containing billions of nucleotides. These programs can compensate for mutations (exchanged, deleted or inserted bases) in the DNA sequence, in order to identify sequences that are related, but not identical. A variant of this sequence alignment is used in the sequencing process itself. The so-called shotgun sequencing technique (which was used, for example, by The Institute for Genomic Research to sequence the first bacterial genome, Haemophilus influenza) does not give a sequential list of nucleotides, but instead the sequences of thousands of small DNA fragments (each about 600-800 nucleotides long). The ends of these fragments overlap and, when aligned in the right way, make up the complete genome. Shotgun sequencing yields sequence data quickly, but the task of assembling the fragments can be quite complicated for larger genomes. In the case of the Human Genome Project, it took several months of CPU time (on a circa-2000 vintage DEC Alpha computer) to assemble the fragments. Shotgun sequencing is the method of choice for virtually all genomes sequenced today, and genome assembly algorithms are a critical area of bioinformatics research.

Another aspect of bioinformatics in sequence analysis is the automatic search for genes and regulatory sequences within a genome. Not all of the nucleotides within a genome are genes. Within the genome of higher organisms, large parts of the DNA do not serve any obvious purpose. This so-called junk DNA may, however, contain unrecognized functional elements. Bioinformatics helps to bridge the gap between genome and proteome projects--for example, in the use of DNA sequences for protein identification.

Genome annotation

In the context of genomics, *annotation* is the process of marking the genes and other biological features in a DNA sequence. The first genome annotation software system was designed in 1995 by Owen White, who was part of the team that sequenced and analyzed the first genome of a free-living organism to be decoded, the bacterium Haemophilus influenzae. Dr. White built a software system to find the genes (places in the DNA sequence that encode a protein), the transfer RNA, and other features, and to make initial assignments of function to those genes. Most current genome annotation systems work similarly, but the programs available for analysis of genomic DNA are constantly changing and improving.

Computational evolutionary biology

Evolutionary biology is the study of the origin and descent of species, as well as their change over time. Informatics has assisted evolutionary biologists in several key ways; it has enabled researchers to:

- trace the evolution of a large number of organisms by measuring changes in their DNA, rather than through physical taxonomy or physiological observations alone,

- more recently, compare entire genomes, which permits the study of more complex evolutionary events, such as gene duplication, lateral gene transfer, and the prediction of bacterial speciation factors,
- build complex computational models of populations to predict the outcome of the system over time
- track and share information on an increasingly large number of species and organisms

Future work endeavours to reconstruct the now more complex tree of life.

The area of research within computer science that uses genetic algorithms is sometimes confused with computational evolutionary biology, but the two areas are unrelated.

Measuring biodiversity

Biodiversity of an ecosystem might be defined as the total genomic complement of a particular environment, from all of the species present, whether it is a biofilm in an abandoned mine, a drop of sea water, a scoop of soil, or the entire biosphere of the planet Earth. Databases are used to collect the species names, descriptions, distributions, genetic information, status and size of populations, habitat needs, and how each organism interacts with other species. Specialized software programs are used to find, visualize, and analyze the information, and most importantly, communicate it to other people. Computer simulations model such things as population dynamics, or calculate the cumulative genetic health of a breeding pool (in agriculture) or endangered population (in conservation). One very exciting potential of this field is that entire DNA sequences, or genomes of endangered species can be preserved, allowing the results of Nature's genetic experiment to be remembered in silico, and possibly reused in the future, even if that species is eventually lost.

Analysis of gene expression

The expression of many genes can be determined by measuring mRNA levels with multiple techniques including microarrays, expressed cDNA sequence tag (EST) sequencing, serial analysis of gene expression (SAGE) tag sequencing, massively parallel signature sequencing (MPSS), or various applications of multiplexed in-situ hybridization. All of these techniques are extremely noise-prone and/or subject to bias in the biological measurement, and a major research area in computational biology involves developing statistical tools to separate signal from noise in high-throughput gene expression studies. Such studies are often used to determine the genes implicated in a disorder: one might compare microarray data from cancerous epithelial cells to data from non-cancerous cells to determine the transcripts that are up-regulated and down-regulated in a particular population of cancer cells.

Analysis of regulation

Regulation is the complex orchestration of events starting with an extra-cellular signal and ultimately leading to an increase or decrease in the activity of one or more protein

molecules. Bioinformatics techniques have been applied to explore various steps in this process. For example, promoter analysis involves the elucidation and study of sequence motifs in the genomic region surrounding the coding region of a gene. These motifs influence the extent to which that region is transcribed into mRNA. Expression data can be used to infer gene regulation: one might compare microarray data from a wide variety of states of an organism to form hypotheses about the genes involved in each state. In a single-cell organism, one might compare stages of the cell cycle, along with various stress conditions (heat shock, starvation, etc.). One can then apply clustering algorithms to that expression data to determine which genes are co-expressed. For example, the upstream regions (promoters) of co-expressed genes can be searched for over-represented regulatory elements.

Analysis of protein expression

Protein microarrays and high throughput (HT) mass spectrometry (MS) can provide a snapshot of the proteins present in a biological sample. Bioinformatics is very much involved in making sense of protein microarray and HT MS data; the former approach faces similar problems as with microarrays targeted at mRNA, the latter involves the problem of matching large amounts of mass data against predicted masses from protein sequence databases, and the complicated statistical analysis of samples where multiple, but incomplete peptides from each protein are detected.

Analysis of mutations in cancer

Massive sequencing efforts are currently underway to identify point mutations in a variety of genes in cancer. The sheer volume of data produced requires automated systems to read sequence data, and to compare the sequencing results to the known sequence of the human genome, including known germline polymorphisms.

Oligonucleotide microarrays, including comparative genomic hybridization and single nucleotide polymorphism arrays, able to probe simultaneously up to several hundred thousand sites throughout the genome are being used to identify chromosomal gains and losses in cancer. Hidden Markov model and change-point analysis methods are being developed to infer real copy number changes from often noisy data. Further informatics approaches are being developed to understand the implications of lesions found to be recurrent across many tumors.

Some modern tools (e.g. Quantum 3.1) provide tool for changing the protein sequence at specific sites through alterations to its amino acids and predict changes in the bioactivity after mutations.

Prediction of protein structure

Protein structure prediction is another important application of bioinformatics. The amino acid sequence of a protein, the so-called primary structure, can be easily determined from the sequence on the gene that codes for it. In the vast majority of cases, this primary

structure uniquely determines a structure in its native environment. (Of course, there are exceptions, such as the bovine spongiform encephalopathy - aka Mad Cow Disease - prion.) Knowledge of this structure is vital in understanding the function of the protein. For lack of better terms, structural information is usually classified as one of secondary, tertiary and quaternary structure. A viable general solution to such predictions remains an open problem. As of now, most efforts have been directed towards heuristics that work most of the time.

One of the key ideas in bioinformatics is the notion of homology. In the genomic branch of bioinformatics, homology is used to predict the function of a gene: if the sequence of gene A, whose function is known, is homologous to the sequence of gene B, whose function is unknown, one could infer that B may share A's function. In the structural branch of bioinformatics, homology is used to determine which parts of a protein are important in structure formation and interaction with other proteins. In a technique called homology modelling, this information is used to predict the structure of a protein once the structure of a homologous protein is known. This currently remains the only way to predict protein structures reliably.

One example of this is the similar protein homology between haemoglobin in humans and the haemoglobin in legumes (leghemoglobin). Both serve the same purpose of transporting oxygen in the organism. Though both of these proteins have completely different amino acid sequences, their protein structures are virtually identical, which reflects their near identical purposes.

Other techniques for predicting protein structure include protein threading and de novo (from scratch) physics-based modeling.

Comparative genomics

The core of comparative genome analysis is the establishment of the correspondence between genes (orthology analysis) or other genomic features in different organisms. It is these intergenomic maps that make it possible to trace the evolutionary processes responsible for the divergence of two genomes. A multitude of evolutionary events acting at various organizational levels shape genome evolution. At the lowest level, point mutations affect individual nucleotides. At a higher level, large chromosomal segments undergo duplication, lateral transfer, inversion, transposition, deletion and insertion. Ultimately, whole genomes are involved in processes of hybridization, polyploidization and endosymbiosis, often leading to rapid speciation. The complexity of genome evolution poses many exciting challenges to developers of mathematical models and algorithms, who have recourse to a spectra of algorithmic, statistical and mathematical techniques, ranging from exact, heuristics, fixed parameter and approximation algorithms for problems based on parsimony models to Markov Chain Monte Carlo algorithms for Bayesian analysis of problems based on probabilistic models.

Many of these studies are based on the homology detection and protein families computation.

Modeling biological systems

Systems biology involves the use of computer simulations of cellular subsystems (such as the networks of metabolites and enzymes which comprise metabolism, signal transduction pathways and gene regulatory networks) to both analyze and visualize the complex connections of these cellular processes. Artificial life or virtual evolution attempts to understand evolutionary processes via the computer simulation of simple (artificial) life forms.

High-throughput image analysis

Computational technologies are used to accelerate or fully automate the processing, quantification and analysis of large amounts of high-information-content biomedical imagery. Modern image analysis systems augment an observer's ability to make measurements from a large or complex set of images, by improving accuracy, objectivity, or speed. A fully developed analysis system may completely replace the observer. Although these systems are not unique to biomedical imagery, biomedical imaging is becoming more important for both diagnostics and research. Some examples are:

- high-throughput and high-fidelity quantification and sub-cellular localization (high-content screening, cytohistopathology)
- morphometrics
- clinical image analysis and visualization
- determining the real-time air-flow patterns in breathing lungs of living animals
- quantifying occlusion size in real-time imagery from the development of and recovery during arterial injury
- making behavioural observations from extended video recordings of laboratory animals
- infrared measurements for metabolic activity determination

Software tools

First generation bioinformatics tools consisted of applications, usually with a text-based interface, which performed a specific task well. The computational biology tool best-known among biologists is probably BLAST, an algorithm for searching large databases of protein or DNA sequences. The NCBI provides a popular web-based implementation that searches their massive sequence databases. Also fairly early on, due to the amassing of sequence and annotation data, keyword search engines which were able to resolve gene and protein synonyms were important. In these early days, computer scripting languages such as Perl and Python were often used to interface with biological databases and parse output from bioinformatics programs written in languages such as C or C++, and much legacy code is still in use today. Today, many other languages are used to author excellent software, and communities of bioinformatics programmers have set up free open source bioinformatics projects to develop and distribute the tools and modules they produce.

As the data sources expanded and diversified, both in content and geography, bioinformatic meta search engines, such as Sequence profiling tools, emerged to help find relevant information from several databases. These meta search engines might index data from a local server or even from a panel of third party services.

More recently, SOAP-based interfaces have been developed for a wide variety of bioinformatics applications allowing an application running on one computer in one part of the world to use algorithms, data and computing resources on servers in other parts of the world. A large availability of these SOAP-based bioinformatics web services, along with the open source bioinformatics collections, lead to the next generation of bioinformatics tools: the integrated bioinformatics platform. These tools range from a collection of standalone tools with a common data format under a single, slick standalone or web-based interface, to integrative and extensible bioinformatics workflow development environments.

An interesting novel direction for bioinformatics applications is illustrated by Q-Pharm's Quantum 3.1, an example of the bioinformatics post-QSAR technology applying quantum and molecular physics instead of statistical methods.

See also

- Pharmaceutical company

Related fields

- applied mathematics — artificial intelligence — biology — computer science — informatics — mathematical biology — theoretical biology — Scientific computing — cheminformatics — neuroinformatics — computational science — Systems biology — statistics

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Genetic algorithms

A *genetic algorithm* is a search technique used in computing to find true or approximate solutions to optimization and search problems, and is often abbreviated as GA. Genetic algorithms are categorized as global search heuristics. Genetic algorithms are a particular class of evolutionary algorithms that use techniques inspired by evolutionary biology such as inheritance, mutation, selection, and crossover (also called recombination).

Genetic algorithms are implemented as a computer simulation in which a population of abstract representations (called chromosomes or the genotype or the genome) of candidate solutions (called individuals, creatures, or phenotypes) to an optimization problem evolves toward better solutions. Traditionally, solutions are represented in binary as strings of 0s and 1s, but other encodings are also possible. The evolution usually starts from a population of randomly generated individuals and happens in generations. In each generation, the fitness of every individual in the population is evaluated, multiple individuals are stochastically selected from the current population (based on their fitness), and modified (recombined and possibly mutated) to form a new population. The new population is then used in the next iteration of the algorithm.

Genetic algorithms find application in computer science, engineering, economics,chemistry, physics, mathematics and other fields.

GA procedure

A typical genetic algorithm requires two things to be defined:

1. a genetic representation of the solution domain,
2. a fitness function to evaluate the solution domain.

A standard representation of the solution is as an array of bits. Arrays of other types and structures can be used in essentially the same way. The main property that makes these genetic representations convenient is that their parts are easily aligned due to their fixed size, that facilitates simple crossover operation. Variable length representations were also used, but crossover implementation is more complex in this case. Tree-like representations are explored in Genetic programming and free-form representations are explored in HBGA.

The fitness function is defined over the genetic representation and measures the quality of the represented solution. The fitness function is always problem dependent. For instance, in the knapsack problem we want to maximize the total value of objects that we can put in a knapsack of some fixed capacity. A representation of a solution might be an array of bits, where each bit represents a different object, and the value of the bit (0 or 1) represents whether or not the object is in the knapsack. Not every such representation is valid, as the size of objects may exceed the capacity of the knapsack. The fitness of the solution is the sum of values of all objects in the knapsack if the representation is valid, or 0 otherwise. In some problems, it is hard or even impossible to define the fitness expression; in these cases, interactive genetic algorithms are used.

Once we have the genetic representation and the fitness function defined, GA proceeds to initialize a population of solutions randomly, then improve it through repetitive application of mutation, crossover, and selection operators.

Initialization

Initially many individual solutions are randomly generated to form an initial population. The population size depends on the nature of the problem, but typically contains several hundreds or thousands of possible solutions. Traditionally, the population is generated randomly, covering the entire range of possible solutions (the search space). Occasionally, the solutions may be "seeded" in areas where optimal solutions are likely to be found.

Selection

During each successive epoch, a proportion of the existing population is selected to breed a new generation. Individual solutions are selected through a fitness-based process, where fitter solutions (as measured by a fitness function) are typically more likely to be selected. Certain selection methods rate the fitness of each solution and preferentially select the best solutions. Other methods rate only a random sample of the population, as this process may be very time-consuming.

Most functions are stochastic and designed so that a small proportion of less fit solutions are selected. This helps keep the diversity of the population large, preventing premature convergence on poor solutions. Popular and well-studied selection methods include roulette wheel selection and tournament selection.

Reproduction

The next step is to generate a second generation population of solutions from those selected through genetic operators: crossover (also called recombination), and/or mutation.

For each new solution to be produced, a pair of "parent" solutions is selected for breeding from the pool selected previously. By producing a "child" solution using the above methods of crossover and mutation, a new solution is created which typically shares many of the characteristics of its "parents". New parents are selected for each child, and the process continues until a new population of solutions of appropriate size is generated.

These processes ultimately result in the next generation population of chromosomes that is different from the initial generation. Generally the average fitness will have increased by this procedure for the population, since only the best organisms from the first generation are selected for breeding, along with a small proportion of less fit solutions, for reasons already mentioned above.

Termination

This generational process is repeated until a termination condition has been reached. Common terminating conditions are

- A solution is found that satisfies minimum criteria
- Fixed number of generations reached
- Allocated budget (computation time/money) reached
- The highest ranking solution's fitness is reaching or has reached a plateau such that successive iterations no longer produce better results
- Manual inspection
- Combinations of the above

Pseudo-code algorithm

Choose initial population Evaluate the fitnesses of individuals in the population Repeat Select best-ranking individuals to reproduce Breed new generation through crossover and mutation (genetic operations) and give birth to offspring Evaluate the individual fitnesses of the offspring Replace worst ranked part of population with offspring Until terminating condition

Observations

There are several general observations about the generation of solutions via a genetic algorithm:

- In many problems with sufficient complexity, GAs may have a tendency to converge towards local optima rather than the global optimum of the problem. The likelihood of this occurring depends on the shape of the fitness landscape: certain problems may provide an easy ascent towards a global optimum, others may make it easier for the function to find the local optima. This problem may be alleviated by using a different fitness function, increasing the rate of mutation, or by using selection techniques that maintain a diverse population of solutions.
- Operating on dynamic data sets is difficult, as genomes begin to converge early on towards solutions which may no longer be valid for later data. Several methods have been proposed to remedy this by increasing genetic diversity somehow and preventing early convergence, either by increasing the probability of mutation when the solution quality drops (called triggered hypermutation), or by occasionally introducing entirely new, randomly

generated elements into the gene pool (called random immigrants). Recent research has also shown the benefits of using biological exaptation (or preadaptation) in solving this problem.

- GAs cannot effectively solve problems in which the only fitness measure is right/wrong, as there is no way to converge on the solution. (No hill to climb). In these cases, a random search may find a solution as quickly as a GA.
- Selection is clearly an important genetic operator, but opinion is divided over the importance of crossover versus mutation. Some argue that crossover is the most important, while mutation is only necessary to ensure that potential solutions are not lost. Others argue that crossover in a largely uniform population only serves to propagate innovations originally found by mutation, and in a non-uniform population crossover is nearly always equivalent to a very large mutation (which is likely to be catastrophic).
- Often, GAs can rapidly locate good solutions, even for difficult search spaces.
- For specific optimization problems and problem instantiations, simpler optimization algorithms may find better solutions than genetic algorithms (given the same amount of computation time). Alternative and complementary algorithms include simulated annealing, hill climbing, and swarm intelligence (e.g.: ant colony optimization, particle swarm optimization).
- As with all current machine learning problems it is worth tuning the parameters such as mutation probability, recombination probability and population size to find reasonable settings for the problem class being worked on. A very small mutation rate may lead to genetic drift (which is non-ergodic in nature) or premature convergence of the genetic algorithm in a local optimum. A mutation rate that is too high may lead to loss of good solutions. There are theoretical but not yet practical upper and lower bounds for these parameters that can help guide selection.
- The implementation and evaluation of the fitness function is an important factor in the speed and efficiency of the algorithm.

Variants

The simplest algorithm represents each chromosome as a bit string. Typically, numeric parameters can be represented by integers, though it is possible to use floating point representations. The basic algorithm performs crossover and mutation at the bit level. Other variants treat the chromosome as a list of numbers which are indexes into an instruction table, nodes in a linked list, hashes, objects, or any other imaginable data structure. Crossover and mutation are performed so as to respect data element boundaries. For most data types, specific variation operators can be designed. Different chromosomal data types seem to work better or worse for different specific problem domains.

When bit strings representations of integers are used, Gray coding is often employed. In this way, small changes in the integer can be readily effected through mutations or crossovers. This has been found to help prevent premature convergence at so called

Hamming walls, in which too many simultaneous mutations (or crossover events) must occur in order to change the chromosome to a better solution.

Other approaches involve using arrays of real-valued numbers instead of bit strings to represent chromosomes. Theoretically, the smaller the alphabet, the better the performance, but paradoxically, good results have been obtained from using real-valued chromosomes.

A slight, but very successful variant of the general process of constructing a new population is to allow some of the better organisms from the current generation to carry over to the next, unaltered. This strategy is known as elitist selection.

Parallel implementations of genetic algorithms come in two flavours. Coarse grained parallel genetic algorithms assume a population on each of the computer nodes and migration of individuals among the nodes. Fine grained parallel genetic algorithms assume an individual on each processor node which acts with neighboring individuals for selection and reproduction. Other variants, like genetic algorithms for online optimization problems, introduce time-dependence or noise in the fitness function.

Problem domains

Problems which appear to be particularly appropriate for solution by genetic algorithms include timetabling and scheduling problems, and many scheduling software packages are based on GAs. GAs have also been applied to engineering. Genetic algorithms are often applied as an approach to solve global optimization problems.

As a general rule of thumb genetic algorithms might be useful in problem domains that have a complex fitness landscape as recombination is designed to move the population away from local optima that a traditional hill climbing algorithm might get stuck in.

History

Computer simulations of evolution started with Nils Aall Barricelli in 1954. Barricelli was simulating the evolution of automata that played a simple card game. Starting in 1957, the Australian quantitative geneticist Alex Fraser published a series of papers on simulation of artificial selection of organisms with multiple loci controlling a measurable trait. From these beginnings, computer simulation of evolution by biologists became more common in the early 1960s, and the methods were described in books by Fraser and Burnell (1970) and Crosby (1973). Many early papers are reprinted by Fogel (1998).

Although Barricelli had also used evolutionary simulation as a general optimization method, genetic algorithms became a widely recognized optimization method as a result of the work of John Holland in the early 1970s, and particularly his 1975 book. His work originated with studies of cellular automata, conducted by Holland and his colleagues at the University of Michigan. Research in GAs remained largely theoretical until the mid-1980s, when The First International Conference on Genetic Algorithms was held at The University of Illinois. As academic interest grew, the dramatic increase in desktop computational power allowed for practical application of the new technique. In 1989, The New York Times writer John Markoff wrote about Evolver, the first commercially available desktop genetic algorithm. Custom computer applications began to emerge in a wide variety of fields, and these algorithms are now used by a majority of Fortune 500 companies to solve difficult

scheduling, data fitting, trend spotting and budgeting problems, and virtually any other type of combinatorial optimization problem.

Related techniques

- Ant colony optimization (ACO) uses many ants (or agents) to traverse the solution space and find locally productive areas. While usually inferior to genetic algorithms and other forms of local search, it is able to produce results in problems where no global or up-to-date perspective can be obtained, and thus the other methods cannot be applied.
- Bacteriologic Algorithms (BA) inspired by evolutionary ecology and, more particularly, bacteriologic adaptation. Evolutionary ecology is the study of living organisms in the context of their environment, with the aim of discovering how they adapt. Its basic concept is that in a heterogeneous environment, you can't find one individual that fits the whole environment. So, you need to reason at the population level. BAs have shown better results than GAs on problems such as complex positioning problems (antennas for cell phones, urban planning, and so on) or data mining
- Cross-entropy method The Cross-entropy (CE) method generates candidates solutions via a parameterized probability distribution. The parameters are updated via cross-entropy minimization, so as to generate better samples in the next iteration.
- Evolution strategies (ES) evolve linear individuals by means of mutation. ES algorithms are designed particulary to solve problems in the real-value domain.
- Extremal optimization (EO) Unlike GAs, which work with a population of candidate solutions, EO evolves a single solution and makes local modifications to the worst components. This requires that a suitable representation be selected which permits individual solution components to be assigned a quality measure ("fitness"). The governing principle behind this algorithm is that of emergent improvement through selectively removing low-quality components and replacing them with a randomly selected component. This is decidedly at odds with a GA that selects good solutions in an attempt to make better solutions.
- Genetic programming (GP) is a related technique popularized by John Koza in which computer programs, rather than function parameters, are optimized. Genetic programming often uses tree-based internal data structures to represent the computer programs for adaptation instead of the list structures typical of genetic algorithms.
- Interactive genetic algorithms (IGA) are genetic algorithms that use human evaluation. They are usually applied to domains where it is hard to design a computational fitness function, for example, evolving images, music, artistic designs and forms to fit users' aesthetic preference.
- Memetic algorithm (MA), also called hybrid genetic algorithm among others, is a relatively new evolutionary method where local search is applied

during the evolutionary cycle. The idea of memetic algorithms comes from memes, which–unlike genes–can adapt themselves. In some problem areas they are shown to be more efficient than traditional evolutionary algorithms.

- Simulated annealing (SA) is a related global optimization technique that traverses the search space by testing random mutations on an individual solution. A mutation that increases fitness is always accepted. A mutation that lowers fitness is accepted probabilistically based on the difference in fitness and a decreasing temperature parameter. In SA parlance, one speaks of seeking the lowest energy instead of the maximum fitness. SA can also be used within a standard GA algorithm by starting with a relatively high rate of mutation and decreasing it over time along a given schedule.
- Stochastic optimization is an umbrella set of methods that includes GAs and numerous other approaches.
- Tabu search (TS) is similar to Simulated Annealing in that both traverse the solution space by testing mutations of an individual solution. While simulated annealing generates only one mutated solution, tabu search generates many mutated solutions and moves to the solution with the lowest energy of those generated. In order to prevent cycling and encourage greater movement through the solution space, a tabu list is maintained of partial or complete solutions. It is forbidden to move to a solution that contains elements of the tabu list, which is updated as the solution traverses the solution space.

Building block hypothesis

[Goldberg, 1989, page 41], talking of binary bit string genetic algorithms, says:

Short, low order, and highly fit schemata are sampled, recombined [crossed over], and resampled to form strings of potentially higher fitness. In a way, by working with these particular schemata [the building blocks], we have reduced the complexity of our problem; instead of building high-performance strings by trying every conceivable combination, we construct better and better strings from the best partial solutions of past samplings. Just as a child creates magnificent fortresses through the arrangement of simple blocks of wood [building blocks], so does a genetic algorithm seek near optimal performance through the juxtaposition of short, low-order, high-performance schemata, or building blocks.

Note [Goldberg, 1989] suggests that building blocks are highly fit schemata with only a few defined bits (low order), and that these are close together (short).

Applications

- Artificial Creativity

Automated design, including research on composite material design and multi-objective design of automotive components for crashworthiness, weight savings, and other characteristics.

Automated design of mechatronic systems using bond graphs and genetic

programming (NSF).
Automated design of industrial equipment using catalogs of exemplar lever patterns.
Calculation of Bound states and Local-density approximations.
Chemical kinetics (gas and solid phases)
Configuration applications, particularly physics applications of optimal molecule configurations for particular systems like C60 (buckyballs).
Container loading optimization.
Code-breaking, using the GA to search large solution spaces of ciphers for the one correct decryption.
Design of water distribution systems.
Distributed computer network topologies.
Electronic circuit design, known as Evolvable hardware.
File allocation for a distributed system.
JGAP: Java Genetic Algorithms Package, also includes support for Genetic Programming
Parallelization of GAs/GPs including use of hierarchical decomposition of problem domains and design spaces nesting of irregular shapes using feature matching and GAs.
Game Theory Equilibrium Resolution.
Learning Robot behavior using Genetic Algorithms.
Learning fuzzy rule base using genetic algorithms.
Linguistic analysis, including Grammar Induction and other aspects of Natural Language Processing (NLP) such as word sense disambiguation.
Mobile communications infrastructure optimization.
Molecular Structure Optimization (Chemistry).
Multiple population topologies and interchange methodologies.
Optimisation of data compression systems, for example using wavelets.
Protein folding and protein/ligand docking.
Plant floor layout.
Representing rational agents in economic models such as the cobweb model.
Scheduling applications, including job-shop scheduling. The objective being to schedule jobs in a sequence dependent or non-sequence dependent setup environment in order to maximize the volume of production while minimizing penalties such as tardiness.
Software engineering
Solving the machine-component grouping problem required for cellular manufacturing systems.
Tactical asset allocation and international equity strategies.
Timetabling problems, such as designing a non-conflicting class timetable for a large university.
Training artificial neural networks when pre-classified training examples are not readily obtainable (neuroevolution).
Traveling Salesman Problem.
Robot learning, obstacle avoidance.

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Bioluminescence

Bioluminescence is the production and emission of light by a living organism as the result of a chemical reaction during which chemical energy is converted to light energy. The name originates from the Greek bios for "living" and the Latin lumen "light". Bioluminescence may be generated by symbiotic organisms carried within a larger organism. It is generated by an enzyme-catalyzed chemoluminescence reaction, wherein the pigment luciferin is oxidised by the enzyme luciferase. Adenosine triphosphate (ATP) is involved in most instances. The chemical reaction can occur either within or outside of the cell. In bacteria, the expression of genes related to bioluminescence is controlled by an operon called the lux operon.

Characteristics of the phenomenon

Bioluminescence is a form of luminescence, or "cold light" emission; less than 20% of the light generates thermal radiation. It should not be confused with fluorescence, phosphorescence or refraction of light.

Ninety percent of deep-sea marine life is estimated to produce bioluminescence in one form or another. Most marine light-emission belongs in the blue and green light spectrum, the wavelengths that can transmit through water most easily. However, certain loose jawed fish emit red and infrared light.

Non-marine bioluminescence is less widely distributed, but a larger variety in colours is seen. The two best-known forms of land bioluminescence are fireflies and New Zealand glow worms. Other insects, insect larvae, annelids, arachnids and even species of fungi have been noted to possess bioluminescent abilities.

Most forms of bioluminescence are lighter (or only exist) at night, following a circadian rhythm.

Adaptations for bioluminescence

There are four main accepted theories for the evolution of bioluminescent traits:

1. Camouflage
2. Attraction
3. Repulsion
4. Communication

Attraction

Bioluminescence is used as a lure to attract prey by several deep sea fish such as the anglerfish. A dangling appendage that extends from the head of the fish attracts small

animals to within striking distance of the fish. Some fish, however, utilize a non-bioluminescent lure.

The cookiecutter shark uses bioluminescence for camouflage, but a small patch on its underbelly remains dark and appears as a small fish to large predatory fish like tuna and mackerel. When these fish try to consume the "small fish", they are bitten by the shark.

Dinoflagellates have an interesting twist on this mechanism. When a predator of plankton is sensed through motion in the water, the dinoflagellate luminesces. This in turn attracts even larger predators which will consume the would-be predator of the dinoflagellate.

The attraction of mates is another proposed mechanism of bioluminescent action. This is seen actively in fireflies who utilize periodic flashing in their abdomens to attract mates in the mating season. In the marine environment this has only been well-documented in certain small crustacean called ostracod. It has been suggested that pheromones may be used for long-distance communication, and bioluminescent used at close range to "home in" on the target.

The honey mushroom attracts insects using bioluminescence, hoping the insects will help disseminate the fungus' spores into the environment.

Repulsion

Certain squid and small crustaceans utilize bioluminescent chemical mixtures, or bioluminescent bacterial slurries in the same way as many squid use ink. A cloud of luminescence is expulsed, confusing or repelling a potential predator while the squid or crustacean escapes to safety.

Communication

Bioluminescence is thought to play a direct role in communication between bacteria. It promotes the symbiotic induction of bacteria into host species, and may play a role in colony aggregation.

Biotechnology

Bioluminescent organisms are a target for many areas of research. Luciferase systems are widely used in the field of genetic engineering as reporter genes (see picture left). Luciferase systems have also been harnessed for biomedical research using bioluminescence imaging.

Vibrio symbiosis with numerous marine invertebrates and fish, namely the Hawaiian bobtail squid (Euprymna scolopes) is a key experimental model for symbiosis, quorum sensing, and bioluminescence.

The structure of photophores, the light producing organs in bioluminescent organisms, are being investigated by industrial designers.

Some proposed applications of engineered bioluminescence include:

- Christmas trees that don't need lights, reducing dangerous electronics
- glowing trees to line highways to save government electricity bills

- agricultural crops and domestic plants that luminesce when they need watering
- new methods for detecting bacterial contamination of meats and other foods
- bio-identifiers for escaped convicts and mental patients
- detecting bacterial species in suspicious corpses
- novelty pets that bioluminesce (rabbits, mice, fish etc.)

Organisms that bioluminesce

All cells produce some form of bioluminescence within the electromagnetic spectrum, but most is neither visible nor noticeable to the naked eye. Every organism's bioluminescence is unique in wavelength, duration, timing and regularity of flashes. Below follows a list of organisms which have been observed to have visible bioluminescence.

Non-marine organisms

- certain arthropods
  - fireflies
  - glow worms
    - railroad worms
  - certain mycetophilid flies

certain centipedes
certain millipedes

- annelids
- Mushrooms (see Foxfire)
  - Jack O'Lantern mushroom

Honey mushroom
Panellus stipticus
several species of Mycena

Fish

- cookie cutter shark

Marine hatchetfish
Anglerfish
Flashlight fish
Pineconefish
Porichthys
Beebe's monster
Gulper Eel

Marine invertebrates

- many cnidarians
  - Sea pens

coral

Aequorea victoria, a jellyfish

- Ctenophores or "comb jellies"

certain echinoderms

certain nudibranchs

certain clams

- certain crustaceans
  - ostracods

krill

- certain Octopuses
  - Bolitaenidae
- certain squid
  - the order Teuthida

Colossal Squid

Mastigoteuthidae

Sepiolidae

Firefly squid

Plankton and microbes

- Dinoflagellates

Vibrionaceae (e.g. Vibrio fischeri, Vibrio harveyi, Vibrio phosphoreum)

Biotechnology products

Antibiotics | Monoclonal antibodies | Recombinant proteins | Acetone

Recombinant proteins

Recombinant DNA (sometimes *rDNA*) is an artificial DNA sequence resulting from the combining of two other DNA sequences in a plasmid. A *recombinant protein* is a protein produced by an organism after the relevant DNA is inserted into its genome (that is, by a genetically modified organism). This recombines the DNA of two different organisms.

Recombinant DNA technique was discovered by Stanley Cohen and Herbert Boyer in 1973, Nov 1973 publication of “Construction of Biologically Functional Bacterial Plasmids in vitro”, this paper described a technique to isolate and amplify genes, or DNA segments, and insert them into another cell with precision. Recombinant DNA technology was made possible by the discovery of restriction endonucleases by Werner Arber, Daniel Nathans, and Hamilton Smith, for which they received the 1978 Nobel Prize in Medicine.

The term *recombinant DNA* refers to a new combination of DNA molecules that are not found together naturally. Although processes such as crossing over technically produce recombinant DNA, the term is generally reserved for DNA produced by joining molecules derived from different biological sources.

Contents

Uses

Recombinant DNA is used for genetic transformation to produce genetically modified organisms. Some examples of recombinant DNA products are peptide hormone medications including insulin, growth hormone, and oxytocin. Vaccines can also be produced using recombinant processes. The organism most commonly used is Escherichia coli.

Plasmids and recombinant DNA technology

Plasmids are extranuclear fragments of DNA present in some bacteria. A plasmid can transfer genetic material to another bacterium, allowing it to express the transmitted gene(s). Restriction enzymes which cut sequences of DNA at certain spots are used to splice into a plasmid the DNA sequence for the desired gene. The plasmid is then inserted into a bacterium in order to express the gene and produce the protein coded for by the gene. Large amounts of the protein can be produced in a factory with vats of the genetically engineered bacteria.

Most eukaryotes cannot use circular DNA such as that present in a plasmid. Yeasts are the only (known) exception. In the others, other systems, such as transfection with viruses, are used instead.

Green fluorescent protein

The *green fluorescent protein* (*GFP*) is a protein, comprised of 238 amino acids, from the jellyfish Aequorea victoria that fluoresces green when exposed to blue light. This process takes place when the protein aequorin, also produced by A. victoria, interacts with Ca^{2+} ions thus emitting a blue glow.

The wild-type GFP (wtGFP) from A. victoria has a major excitation peak at a wavelength of 395 nm and a minor one at 475 nm. Its emission peak is at 509 nm which is in the lower green portion of the visible spectrum. The GFP from the sea pansy (Renilla reniformis) has a single major excitation peak at 498 nm.

In cell and molecular biology, the GFP gene is frequently used as a reporter of expression. In modified forms it has been used to make biosensors, and many animals have been created

that express GFP as a proof-of-concept that a gene can be expressed throughout a given organism.

One of the most powerful uses of GFP is to express the protein in small sets of specific cells. This allows researchers to optically detect specific types of cells in vitro (in a dish), or even in vivo (in the living organism). The GFP gene can be introduced into organisms and maintained in their genome through breeding, or local injection with a viral vector can be used to introduce the gene.

Due to this widespread usage different mutants of GFP have been engineered over the last few years by the lab of Roger Tsien and others: some mutants have been produced with increased fluorescence and the protein major excitation peak has been shifted to 490 nm with the peak emission kept at 509 nm (EGFP). Color mutants have been obtained from the GFP gene as well: in particular the cyan fluorescent protein (CFP) and the yellow fluorescent protein (YFP) are two colour variants employed for fluorescence resonance energy transfer (FRET) experiments. Genetically-encoded FRET reporters sensitive to cell signaling molecules, such as calcium or glutamate, protein phosphorylation state, protein complementation, receptor dimerization and other processes provide highly specific optical readouts of cell activity in real time.

EGFP is an enhanced green fluorescent protein which is also a commonly used gene reporter.

It is also worth mentioning that the availability of GFP and its derivatives has thoroughly redefined fluorescence microscopy and the way it is used in cell biology and other biological disciplines. While most small fluorescent molecules such as FITC (fluorescein isothiocyanate) are strongly phototoxic when used in live cells, fluorescent proteins such as GFP are usually much less harmful when illuminated in living cells. This has triggered the development of highly automated live cell fluorescence microscopy systems which can be used to observe cells over time expressing one or more proteins tagged with fluorescent proteins. Analysis of such time lapse movies has redefined the understanding of many biological processes which in the past had been studied using fixed (i.e. dead) material.

To date, many bacteria, yeast and other fungal cells, plant, fly, and mammalian cells have been created using GFP as a marker. Research scientists, from National Taiwan University's Department of Animal Science and Technology also reported the production of three fluorescent pigs in early 2006.

Notes

- Alba, a fluorescent bunny, was created by Eduardo Kac using GFP for purposes of art and social commentary

Growth hormone

Growth hormone (*GH* or *somatotropin*) is a polypeptide hormone synthesised and secreted by the anterior pituitary gland which stimulates growth and cell reproduction in humans and other vertebrate animals.

This article describes human growth hormone physiology, with brief mentions of the diseases of GH deficiency, GH excess (acromegaly and pituitary gigantism), as well as GH treatment, and HGH quackery. Each of these topics is treated more fully in separate articles.

Terminology

Growth hormone (GH) is also called somatropin and somatotropin (British: somatotrophin). hGH refers to human growth hormone and is an abbreviation for human GH measured in the extracts from human pituitary glands. In 1985, biosynthetic human growth hormone replaced pituitary-derived human growth hormone for therapeutic use in the U.S. and elsewhere. Biosynthetic human growth hormone, also referred to as recombinant human growth hormone, is also called somatropin and abbreviated as rhGH. Since the mid-1990s the abbreviation HGH has begun to carry paradoxical connotations, and now rarely refers to real GH used for indicated purposes. See articles on GH treatment and hGH quackery for fuller discussions of GH therapy and the HGH issue.

Structure and gene of the human GH molecule

The genes for human growth hormone are localized in the q22-24 region of chromosome 17 and are closely related to human chorionic somatomammotropin (hCS, also known as placental lactogen) genes. GH, human chorionic somatomammotropin (hCS), and prolactin (PRL) are a group of homologous hormones with growth-promoting and lactogenic activity.

The major isoform of the human growth hormone is a protein of 191 amino acids and a molecular weight of about 22,000 daltons. The structure includes four helices necessary for functional interaction with the GH receptor. GH is structurally and apparently evolutionarily homologous to prolactin and chorionic somatomammotropin. Despite marked structural similarities between growth hormone from different species, only human and primate growth hormones have significant effects in humans.

Secretion of GH

GH is secreted into the blood by the somatotrope cells of the anterior pituitary gland, in larger amounts than any other pituitary hormone. Secretion levels are highest during puberty. The transcription factor PIT-1 stimulates both the development of these cells and their production of GH. Failure of development of these cells, as well as destruction of the anterior pituitary gland, results in GH deficiency.

Peptides released by neurosecretory nuclei of the hypothalamus into the portal venous blood surrounding the pituitary are the major controllers of GH secretion by the somatotropes. Growth hormone releasing hormone (GHRH) from the arcuate nucleus and ghrelin promote GH secretion, and somatostatin from the periventricular nucleus inhibits it. GH secretion is also affected by negative feedback from circulating concentrations of GH and IGF-1.

Although the balance of these stimulating and inhibiting peptides determines GH release, this balance is affected by many physiological stimulators and inhibitors of GH secretion. Stimulators of GH secretion include (among others) J B B , exercise, hypoglycemia, dietary

protein, and estradiol. Inhibitors of GH secretion include dietary carbohydrate and glucocorticoids. In addition to control by endogenous processes, a number of foreign compounds (xenobiotics) are now known to influence GH secretion, highlighting the fact that the GH-IGF axis is an emerging target for certain endocrine disrupting chemicals.

Most of the physiologically important GH secretion occurs as several large pulses or peaks of GH release each day. The plasma concentration of GH during these peaks may range from 5 to 30 ng/mL or more. Peaks typically last from 10 to 30 minutes before returning to basal levels. The largest and most predictable of these GH peaks occurs about an hour after onset of sleep. Otherwise there is wide variation between days and individuals. Between the peaks, basal GH levels are low, usually less than 3 ng/mL for most of the day and night.

The amount and pattern of GH secretion change throughout life. Basal levels are highest in early childhood. The amplitude and frequency of peaks is greatest during the pubertal growth spurt. Healthy children and adolescents average about 8 peaks per 24 hours. Adults average about 5 peaks. Basal levels and the frequency and amplitude of peaks decline throughout adult life.

Several molecular forms of GH circulate. Much of the growth hormone in the circulation is bound to a protein (growth hormone binding protein, GHBP) which is derived from the growth hormone receptor.

Functions of GH

Effects of growth hormone on the tissues of the body can generally be described as anabolic (building up). Like most other protein hormones GH acts by interacting with a specific receptor on the surface of cells.

Height growth in childhood is the best known effect of GH action, and appears to be stimulated by at least two mechanisms. 1. GH directly stimulates division and multiplication of chondrocytes of cartilage. These are the primary cells in the growing ends (epiphyses) of children's long bones (arms, legs, digits). 2. GH also stimulates production of insulin-like growth factor 1 (IGF1, formerly known as somatomedin C), a hormone homologous to proinsulin. The liver is a major target organ of GH for this process, and is the principal site of IGF-1 production. IGF-1 has growth-stimulating effects on a wide variety of tissues. Additional IGF-1 is generated within target tissues, making it apparently both an endocrine and an autocrine/paracrine hormone. IGF-1 will also have stimulatory effects on osteoblast and chondrocyte activity to promote bone growth.

Although height growth is the best known effect of GH, it serves many other metabolic functions as well. GH increases calcium retention, and strengthens and increases the mineralization of bone. It increases muscle mass through the creation of new muscle cells (which differs from hypertrophy), and it also promotes lipolysis, which results in the reduction of adipose tissue (body fat). As well, it increases protein synthesis and stimulates the growth of all internal organs excluding the brain. GH plays a role in fuel homeostasis. GH reduces liver uptake of glucose, an effect that opposes that of insulin. GH also contributes to the maintenance and function of pancreatic islets. GH stimulates the immune system.

Clinical problems: too much and too little

Growth hormone excess: (acromegaly and pituitary gigantism)

The most common disease of GH excess is a pituitary tumor comprised of somatotroph cells of the anterior pituitary. These somatotroph adenomas are benign and grow slowly, gradually producing more and more GH. For years, the principal clinical problems are those of GH excess. Eventually the adenoma may become large enough to cause headaches, impair vision by pressure on the optic nerves, or cause deficiency of other pituitary hormones by displacement.

Prolonged GH excess thickens the bones of the jaw, fingers and toes. Resulting heaviness of the jaw and increased thickness of digits is referred to as acromegaly. Accompanying problems can include pressure on nerves (e.g., carpal tunnel syndrome), muscle weakness, insulin resistance or even a rare form of type 2 diabetes, and reduced sexual function.

GH-secreting tumors are typically recognized in the 5th decade of life. It is extremely rare for such a tumor to occur in childhood, but when it does the excessive GH can cause excessive growth, traditionally referred to as pituitary gigantism.

Surgical removal is the usual treatment for GH-producing tumors. In some circumstances focused radiation or a GH antagonist such as bromocriptine or octreotide may be employed to shrink the tumor or block function.

Growth hormone deficiency (GHD)

Deficiency of GH produces significantly different problems at various ages. In children, growth failure and short stature are the major manifestations of GH deficiency. In adults the effects of deficiency are more subtle, and may include deficiencies of strength, energy, and bone mass, as well as increased cardiovascular risk.

There are many causes of GH deficiency, including mutations of specific genes, congenital malformations involving the hypothalamus and/or pituitary gland, and damage to the pituitary from injury, surgery or disease.

Diagnosis of GH deficiency involves a multiple step diagnostic process, usually culminating in GH stimulation test(s) to see if the patient's pituitary gland will release a pulse of GH when provoked by various stimuli.

GH deficiency is treated by replacing GH. All GH in current use is a biosynthetic version of human GH, manufactured by recombinant DNA technology. As GH is a large protein molecule, it must be injected into subcutaneous tissue (or muscle) to get it into the blood. When the patient has had a long-standing deficiency of GH, benefits of treatment are often dramatic and gratifying and side effects of treatment are rare. Increased growth in childhood can result in dramatically improved adult height.

GH is used as replacement therapy in adults with GH deficiency of either childhood-onset (after completing growth phase) or adult-onset (usually as a result of an acquired pituitary tumor). In these patients, benefits have variably included reduced fat mass, increased lean mass, increased bone density, improved lipid profile, reduced cardiovascular risk factors, and improved psychosocial well-being.

This topic is treated more fully in the articles growth hormone deficiency and growth hormone treatment.

Other GH uses and treatment indications

Many other conditions besides GH deficiency cause poor growth, but growth benefits (height gains) are often poorer than when GH deficiency is treated. Examples of other causes of shortness often treated with growth hormone are Turner syndrome, chronic renal failure, Prader-Willi syndrome, intrauterine growth retardation, and severe idiopathic short stature. Higher ("pharmacologic") doses are required to produce significant acceleration of growth in these conditions, producing blood levels well above physiologic. Despite the higher doses, side effects during treatment are rare, and vary little according to the condition being treated.

Sometimes GH is used for other benefits than height. GH treatment improves muscle strength and slightly reduce body fat in Prader-Willi syndrome, benefits more important to these children than increased height. It has also been shown to help maintain muscle mass in AIDS wasting. GH can also be used in patients with short bowel syndrome to lessen the requirement for intravenous parenteral nutrition.

Uses that are controversial include

- GH treatment to reverse effects of aging in older adults

GH treatment to enhance weight loss in obesity
GH treatment for fibromyalgia
GH treatment for Crohn's disease and ulcerative colitis
GH treatment for idiopathic short stature
GH treatment for bodybuilding or athletic enhancement

Risks and side effects of GH treatment

The possible risks and side effects of GH use are varied. They can occur even when used in "pharmacologic doses." They include:

- swelling of the hands and feet(edema)
- thickening of the bones/jaw
- carpal tunnel syndrome/Arthralgia
- tingling in the extremities
- numbness in the hands and feet
- increased organ growth
- decreased insulin reception
- acromegaly
- decreased thyroid output

History

The identification, purification and later synthesis of growth hormone is associated with Choh Hao Li. The history of GH use, from extraction of GH from human pituitary glands to

the limited catastrophe of Creutzfeldt-Jakob Disease to the expanded use and enormous costs of synthetic GH is outlined in the article on GH treatment.

As of 2005, synthetic growth hormones available in the United States (and their manufacturers) included Nutropin (Genentech), Humatrope (Lilly), Genotropin (Pfizer), Norditropin (Novo), and Saizen (Serono). The products are nearly identical in composition, efficacy, and cost, varying primarily in the formulations and delivery devices. In 2005 an Israeli company, Teva, offered Tev-Tropin in the U.S. at a lower price. Lilly and Alkermes are developing an inhalable version that is in phase III clinical trials as of April, 2006.

HGH quackery

Consumers should understand that use of the term "HGH" by marketers since 1990 is a nearly infallible sign that a product so labeled contains no effective amount of growth hormone. Endocrinologists tend to use other terms, and the specific term HGH is often an indicator of questionable claims or information. For fuller discussion, see HGH quackery.

Luteinizing hormone

Luteinizing hormone beta polypeptide *Identifiers*

Symbol(s) LHB

Entrez 3972

OMIM **152780**

RefSeq NM_000894

UniProt P01229

Other data

Locus Chr. 19 q13.3

Luteinizing hormone (*LH*) is a hormone synthesized and secreted by gonadotropes in the anterior lobe of the pituitary gland. In concert with the other pituitary gonadotropin follicle stimulating hormone (FSH) it is necessary for proper reproductive function. In the female, an acute rise of LH – the *LH surge* – triggers ovulation. In the male, where LH had also been called *Interstitial Cell Stimulating Hormone* (*ICSH*), it stimulates Leydig cell production of testosterone.

Structure

LH is a glycoprotein. Each monomeric unit is a protein molecule with a sugar attached to it; two of these make the full, functional protein. Its structure is similar to the other glycoproteins, FSH, TSH, and hCG. The protein dimer contains 2 polypeptide units, labeled

alpha and beta subunits that are connected by two disulfide bridges. The alpha subunits of LH, FSH, TSH, and hCG are identical, and contain 92 amino acids. The beta subunits vary. LH has a beta subunit of 121 amino acids (LHB) that confers its specific biologic action and is responsible for interaction with the LH receptor. This beta subunit contains the same amino acids in sequence as the beta sub unit of hCG and both stimulate the same receptor, however, the hCG beta subunit contains an additional 24 amino acids, and both hormones differ in the composition of their sugar moieties. The different composition of these oligosaccharides affects bioactivity and speed of degradation. The biologic half-life of LH is 20 minutes, shorter than that of FSH (3-4 hours) or hCG (24 hours).

Genes

The gene for the alpha subunit is located on chromosome 6q12.21. The luteinizing hormone beta-subunit gene is localized in the LHB/CGB gene cluster on chromosome 19q13.32. In contrast to the alpha gene activity, beta LH subunit gene activity is restricted to the pituitary gonadotropic cells. It is regulated by the gonadotropin releasing hormone from the hypothalamus. Inhibin, activin, and sex hormones do not affect genetic activity for the beta subunit production of LH.

Activity

In both males and females, LH is essential for reproduction. In females, at the time of menstruation, FSH initiates follicular growth, specifically affecting granulosa cells. With the rise in estrogens, also LH receptors are expressed on the maturing follicle that produces an increasing amount of estradiol. Eventually at the time of the maturation of the follicle, the estrogen rise leads via the hypothalamic interface to the "positive feed-back" effect, a release of LH over a 24-48 hour. This *LH surge* triggers ovulation hereby not only releasing the egg, but also initiating the conversion of the residual follicle into a corpus luteum that, in turn, produces Progesterone to prepare the endometrium for a possible implantation. LH is necessary to maintain luteal function for the first two weeks. In case of a pregnancy luteal function will be further maintained by the action of hCG from the newly established pregnancy. LH supports thecal cells in the ovary that provide androgens and hormonal precursors for estradiol production.

In the male, LH acts upon the Leydig cell of the testis and is responsible for testosterone production that exerts intratesticular activity in terms of the spermatogenesis and endocrine activity as the "male hormone".

The release of LH at the pituitary gland is controlled by pulses of gonadotropin-releasing hormone (GnRH) from the hypothalamus. Those pulses, in turn, are subject to the estrogen feed-back from the gonads.

Normal levels

LH levels are normally low during childhood and, in women, high after menopause. During the reproductive years typical levels are seen between 5-20 mIU/ml. Physiologic high LH levels are seen during the LH surge (v.s.), typically they last 48 hours.

Ovulation predictor kit (LH kit)

The detection of the LH surge has become useful for people who want to know when ovulation occurs. LH can be detected by urinary ovulation predictor kits (OPK, also LH-kit) that are performed daily around the time ovulation may be expected. The conversion from a negative to a positive reading would suggest that ovulation is about to occur within 24-48 hours. Couples who plan to conceive would time intercourse accordingly. As sperms can stay viable in the woman for several days, such tests are not recommended for contraceptive practices.

Disease States

Relative elevations

In children with precocious puberty of pituitary or central origin, LH and FSH levels may be in the reproductive range and not at the low levels typically for their age.

During the reproductive years, relatively elevated LH are frequently seen in patients with the polycystic ovary syndrome, however it would be unusual to have LH levels outside of the normal reproductive range.

High LH levels

Persistently high LH levels are indicative of situations where the normal restricting feedback from the gonad is absent, leading to an unrestricted pituitary production of both, LH and FSH. While this is typical in the menopause, it is abnormal in the reproductive years. There it may be a sign of:

1. Premature menopause

Gonadal dysgenesis, Turner syndrome
Castration
Swyer syndrome
Certain forms of CAH
Testicular failure

Deficient LH activity

Diminished secretion of LH can result in failure of gonadal function (hypogonadism). This condition is typically manifest in males as failure in production of normal numbers of sperm. In females, amenorrhea is commonly observed. Conditions with very low FSH secretions are:

1. Kallmann syndrome

Hypothalamic suppression
Hypopituitarism
Eating disorder
Hyperprolactinemia
Gonadotropin deficiency

2. Gonadal suppression therapy
    1. GnRH antagonist

GnRH agonist (downregulation)

Availability

LH is available mixed with FSH in the form of Pergonal, and other forms of urinary gonadotropins . More purified forms of urinary gonadotropins may reduce the LH portion in relation to FSH. Recombinant LH is available as lutropin alfa (Luveris®)[1]. All these medications have to be given parenterally. They are commonly in infertility therapy to stimulate follicular development, notably in IVF therapy.

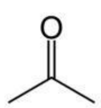
Often, hCG medication is used as an LH substitute as it activates the same receptor. Medically used hCG is derived from urine of pregnant women, less costly, and has a longer half-life than LH.

References

- Mendelian Inheritance in Man (OMIM) 152780, Luteinizing hormone, beta polypeptide; LHB
- Mendelian Inheritance in Man (OMIM) 152790, LH-receptor; LHCGR

1. ^ Luveris information

Acetone



Systematic name Propanone

Other names ^{2}-ketopropane, Dimethyl ketone

Molecular formula CH_3COCH_3

SMILES CC(=O)C

Molar mass 58.09 g/mol

Appearance Colorless liquid

CAS number [67-64-1]

Properties

Density and phase 0.79 g/cm^3, liquid

Solubility in water miscible

Melting point 94.9 °C (178.2 K)

Boiling point 56.3 °C (329.4 K)

Viscosity 0.32 cP at 20 °C

Structure

Molecular shape trigonal planar at C=O

Dipole moment 2.91 D

Hazards

MSDS External MSDS

EU classification Flammable (*F*), Irritant (*Xi*), R11, R36, R66, R67
S-phrases S2, S9, S16, S26
Flash point 20 °C
Autoignition temperature 465 °C
RTECS number AL31500000

Supplementary data page

Structure & properties n, μ_r, etc.

Thermodynamic data Phase behaviour, Solid, liquid, gas

Spectral data UV, IR, NMR, MS

Related compounds

Related ketones Butanone

Related solvents water, Ethanol, Isopropanol, Toluene

Except where noted otherwise, data are given for materials in their standard state (at 25°C, 100 kPa)

In chemistry, *acetone* (also known as *propanone*, *dimethyl ketone*, *2-propanone*, *propan-2-one* and ^{2}*-ketopropane*) is the simplest representative of the ketones.

Acetone is a colorless mobile flammable liquid with melting point at 95.4 °C and boiling point at 56.53 °C. It has a relative density of 0.819 (at 0 °C). It is readily soluble in water, ethanol, ether, etc., and itself serves as an important solvent. The most familiar household use of acetone is as the active ingredient in nail polish remover. Acetone is also used to make plastic, fibers, drugs, and other chemicals.

Uses

An important industrial use for acetone involves its reaction with phenol for the manufacture of bisphenol A. Bisphenol A is an important component of many polymers such as polycarbonates, polyurethanes and epoxy resins. Acetone is also used extensively for the safe transporting and storing of acetylene. Vessels containing a porous material are first filled with acetone followed by acetylene, which dissolves into the acetone. One liter of acetone can dissolve around 250 litres of acetylene.

Acetone is often the primary (or only) component in nail polish remover. Acetone is also used as a superglue remover. It can be used for thinning and cleaning fiberglass resins and epoxies. It is a strong solvent for most plastics and synthetic fibres.

Acetone has been used in the manufacture of cordite. During World War I a new process of producing acetone through bacterial fermentation was developed by Chaim Weizmann, to help the British war effort.

Acetone can also dissolve many plastics, including those used in consumer-targeted Nalgene bottles.

Acetone is also used as a drying agent, due to the readiness with which it binds to water, and its volatility.

Acetone can also be used on the hair. It can be used as a rinse before shampooing to remove build up, oil and hard water minerals.

Uses in universities and professional laboratories

Due to the nonpolar properties of acetone, it has been used in many university labs as a cleanser for nonpolar substances in testtubes after working with nonpolar organic substances (i.e. cyclohexane, cyclohexene). Acetone is squirted directly from a bottle containing the substance onto the glassware and is drained into a specially marked organic waste bucket.

However, care should be used when cleaning testtubes with acetone as acetone is readily absorbed through vinyl or latex gloves and will come in contact with skin where it is absorbed into the skin. If an excessive amount of acetone is splashed onto gloves, remove gloves immediately and wash hands with water before donning a new pair of gloves.

Acetone is very cool to the touch due to its high volatility and will evaporate quickly, making it very useful in drying lab glassware. Avoid inhaling fumes as acetone is an irritant and inhalation may lead to hepatanic effects (causing liver damage). Always use goggles when handling acetone, it can cause permanent eye damage (corneal clouding).

Health effects

Small amounts of acetone are metabolically produced in the body, mainly from fat. In humans, fasting significantly increases its endogenous production (see ketosis). Acetone can be elevated in diabetes. Exposure to exogenous acetone can be chronic due to acetone contamination of water, food (e.g. milk), or the air (acetone is volatile). A number of acute poisoning cases have been described. Relatively speaking, acetone is not a very toxic compound; it can, however, damage the mucosa of the mouth and can irritate and damage skin. Accidental intake of large amounts of acetone may lead to unconsciousness and death.

The effects of long-term exposure to acetone are known mostly from animal studies. Kidney, liver, and nerve damage, increased birth defects, and lowered reproduction ability of males (only) occurred in animals exposed long-term. It is not known if these same effects would be exhibited in humans.

Interestingly, acetone has been shown to have anticonvulsant effects in animal models of epilepsy, in the absence of toxicity, when administered in millimolar concentrations (see: Likhodii et. al., Ann Neurol. 2003;54(2):219-226). It has been hypothesized that the high fat low carbohydrate ketogenic diet used clinically to control drug-resistant epilepsy in children works by elevating acetone in the brain (see Ibid, p. 219).

Cloning

Cloning is the process of creating an identical copy of an original organism or thing. A cloning in the biological sense, therefore, is a molecule, single cell (like bacteria, lymphocytes etc.) or multi-cellular organism that has been directly copied from and is therefore genetically identical to another living organism. Sometimes this term can refer to "natural" clones made either when an organism is asexually reproduced by chance (as with identical twins), but in common parlance, a clone is an identical copy created intentionally.

The term clone is derived from º»É½, the Greek word for "twig". In horticulture, the spelling clon was used until the twentieth century; the final e came into use to indicate the vowel is a "long o" instead of a "short o". Since the term entered the popular lexicon in a more general context, the spelling clone has been used exclusively.

Molecular cloning

Molecular cloning refers to the procedure of isolating a DNA sequence of interest and obtaining multiple copies of it in an organism. Cloning is frequently employed to amplify DNA fragments containing genes, an essential step in their subsequent analysis. Frequently, the term cloning is misleadingly used to refer to the identification of the chromosomal location of a gene associated with a particular phenotype of interest. In practice, localisation of the gene does not always enable one to amplify the relevant genomic sequence.

Cloning of any DNA sequence involves the following four steps: amplification, ligation, transfection, and screening/selection. Initially, the DNA fragment of interest needs to be

amplified (many copies need to be produced). Amplification is commonly achieved by means of PCR. Subsequently, a ligation procedure is employed whereby the amplified fragment is inserted into a vector. The vector (which is frequently circular) is linearised by means of restriction enzymes, and incubated with the fragment of interest under appropriate conditions that allow for ligation. The yield of the ligation is typically low and depends on the procedure employed. Following ligation the vector with the insert of interest is transfected to cells. Most commonly electroporation is employed, although a number of alternative techniques are available, such as chemical sensitivation of cells. Finally, the transfected cells are cultured. As the aforementioned procedures are of particularly low yield, there is the need to identify the cell colonies that have been transfected with the construct of interest containing the desired insertion sequence. Modern cloning vectors include selectable antibiotic resistance markers, which allow only for cells in which the vector has been transfected to grow. However this selection step does not guarantee that the DNA insert is present in the vector. Further investigation of the resulting colonies is required to confirm that cloning was successful. This can be accomplished by means of blue/white screening (±-factor complimentation) on X-gal medium and/or PCR, possibly followed by DNA sequencing.

Genetic cloning

Cloning a cell means to derive a (clonal) population of cells from a single cell. This is an important in vitro procedure when the expansion of a single cell with certain characteristics is desired, for example in the production of gene-targeted ES cells. Most individuals began as a single cell and are therefore the result of clonal expansion in vivo.

Organism

Cloning means to create a new organism with the same genetic information as a cell from an existing one(identical). It is an asexual method of reproduction, where fertilization or inter-gamete contact does not take place. Asexual reproduction (also known as agamogenesis) is a form of reproduction which does not involve meiosis, gamete formation, or fertilization. In laymen's terms, there is only one "parent" involved. This form of reproduction is common among simple organisms such as amoeba and other single-celled organisms, although most plants reproduce asexually as well.

Horticultural

The term clone is used in horticulture to mean all descendants of a single plant, produced by vegetative reproduction or apomixis. Many horticultural plant cultivars are clones, having been derived from a single individual, multiplied by some process other than sexual reproduction. As an example, some European cultivars of grapes represent clones that have been propagated for over two millennia. Other examples are potato and banana. Grafting can be regarded as cloning, since all the shoots and branches coming from the graft are genetically a clone of a single individual, although the root systems may be genetically

genuine examples of cloning in the broader biological sense, as they create genetically identical organisms by biological means, but this particular kind of cloning has not come under ethical scrutiny and is generally treated as an entirely different kind of operation.

Many trees, shrubs, vines, ferns and other herbaceous perennials form clonal colonies. Parts of a large clonal colony often become detached from the parent, termed fragmentation, to form separate individuals. Some plants also form seeds asexually, termed apomixis, e.g. dandelion.

Animals

Cloning exists in nature in some animal species and is referred to as parthenogenesis. An example is the "Little Fire Ant" (Wasmannia auropunctata), which is native to Central and South America but has spread throughout many *tropical* environments.

Reproductive Cloning

Reproductive cloning is a technology used to generate an animal that has the same nuclear DNA as another currently or previously existing animal. Dolly the sheep, was created by reproductive cloning technology. In a process called "somatic cell nuclear transfer" (SCNT), scientists transfer genetic material from the nucleus of a donor adult cell to an egg whose nucleus, and thus its genetic material, has been removed. The reconstructed egg containing the DNA from a donor cell must be treated with chemicals or electric current in order to stimulate cell division. Once the cloned embryo reaches a suitable stage, it is transferred to the uterus of a female host where it continues to develop until birth.

Dolly or any other animal created using nuclear transfer technology is not truly an identical clone of the donor animal. Only the clone's chromosomal or nuclear DNA is the same as the donor. Some of the clone's genetic materials come from the mitochondria in the cytoplasm of the enucleated egg. Mitochondria, which are organelles that serve as power sources to the cell, contain their own short segments of DNA, although this is only 0.01% of the total DNA. Acquired mutations in mitochondrial DNA are believed to play an important role in the aging process.

Also mutations occur with every cell division so no two cells in an individual are identical, nor are clones. Thus, nuclear transfer clones from different maternal lineages are not clones in the strictest sense because the mitochondrial genome is not the same as that of the nucleus donor cell from which it was produced. This may have important implications for cross-species nuclear transfer in which nuclear-mitochondrial incompatibilities may lead to inviability.

Species cloned

The modern cloning techniques involving nuclear transfer have been successfully performed on several species. Landmark experiments in chronological order:

- Tadpole: (1952) Many scientists questioned whether cloning had actually occurred and unpublished experiments by other labs were not able to reproduce the reported results.
 Carp: (1963) In China, embryologist Tong Dizhou cloned a fish. He published the findings in an obscure Chinese science journal which was never translated into English.[1]
 Mice: (1986) was the first successfully cloned mammal; Soviet scientists Chaylakhyan, Veprencev, Sviridova, Nikitin had mice "Masha" cloned. Research was published in the magazine "Biofizika" volume %%%II, issue 5 of 1987.[2]
 Sheep: (1996) From early embryonic cells by Steen Willadsen. Megan and Morag cloned from differentiated embryonic cells in June 1995 and Dolly the sheep in 1997.
 Rhesus Monkey: Tetra (female, January 2000) from embryo splitting
 Cattle: Alpha and Beta (males, 2001) and (2005) Brazil[3]
 Cat: CopyCat "CC" (female, late 2001), Little Nicky, 2004, was the first cat cloned for commercial reasons
 Mule: Idaho Gem, a john mule born 2003-05-04, was the first horse-family clone.
 Horse: Prometea, a Haflinger female born 2003-05-28, was the first horse clone.

During the first several divisions of a fertilized egg, no differentiation occurs and the cells can be separated without harm, but each will grow into an identical individual. This process has been used on cattle for decades to produce hundreds of identical individuals in some cases. This process is not considered cloning, but is called budding. The new individual is not derived from a differentiated cell, but from an undifferentiated egg. There is no way to determine which are the clones and which is the original.

Health aspects

The success rate of cloning has been low: Dolly the sheep was born after 277 eggs were used to create 29 embryos, which only produced three lambs at birth, only one of which lived, Dolly. Seventy calves have been created from 9,000 attempts and one third of them died young; Prometea took 328 attempts, and, more recently, Paris Texas was created after 400 attempts. Notably, although the first clones were frogs, no adult cloned frog has yet been produced from a somatic adult nucleus donor cell.

There were early claims that Dolly the Sheep had accelerated aging. Aging of this type is thought to be due to shortening of telomeres, regions at the tips of chromosomes which prevent genetic threads fraying every time a cell divides. Over time telomeres get worn down until cell-division is no longer possible — this is thought to be a cause of aging. However, subsequent studies showed that, if anything, Dolly's telomere were longer than normal. Dolly died in the year of 2003. Ian Wilmut said that Dolly's early death had nothing to do with cloning but with a respiratory infection common to lambs raised indoors like Dolly.

Consistent with Dolly's telomeres being longer, analysis of the telomeres from cloned cows showed that they were also longer. This suggests clones could live longer life spans although many died young after excessive growth. Researchers think that this could eventually be developed to reverse aging in humans, provided that this is based chiefly on

the shortening of telomeres. Although some work has been performed on telomeres and aging in nuclear transfer clones, the evidence is at an early stage. [4]

Dolly the Sheep

Dolly (1996-07-05 – 2003-02-14), an ewe, was the first mammal to have been successfully cloned from an adult cell (while the mice in USSR was cloned from embryo cell back in 1986). She was cloned at the Roslin Institute in Scotland and lived there until her death when she was 6. Her birth was announced on 1997-02-22.

The name "Dolly" came from a suggestion by Jesse Haase who helped with her birth, in honor of Dolly Parton, because it was a mammary cell that was cloned. The technique that was made famous by her birth is somatic cell nuclear transfer, in which a non-reproductive cell containing a nucleus is placed in a de-nucleated ovum (which then develops into a fetus). When Dolly was cloned in 1996 from a cell taken from a six-year-old ewe, she became the center of much controversy that still exists today.

Dolly's success is truly remarkable because it proved that the genetic material from a specialized adult cell, such as an udder cell programmed to express only those genes needed by udder cells, could be reprogrammed to generate an entire new organism. Before this demonstration, scientists believed that once a cell became specialized as a liver, heart, udder, bone, or any other type of cell, the change was permanent and other unneeded genes in the cell would become inactive. Some scientists believe that errors or incompleteness in the reprogramming process cause the high rates of death, deformity, and disability observed among animal clones.

On 2003-04-09 her stuffed remains were placed at Edinburgh's Royal Museum, part of the National Museums of Scotland.

Ian Wilmut's role in cloning Dolly the sheep is in doubt. In 2006 he admitted under oath in a Scottish court that he did not clone Dolly the Sheep and was not responsible for the scientific breakthrough which made it all possible. He credited Keith Campbell as being the brains behind Dolly the Sheep.

In August 2006, Iranian scientists oversaw the birth of the Middle East’s first cloned animal – a lamb that died minutes after it was born. However, in September 2006, Iranian scientists successfully cloned a sheep, by somatic cell nuclear transfer, at the Royan research institute in Isfahan, Iran’s second cloned lamb is still alive.

Human cloning

Human cloning is the creation of a genetically identical copy of an existing, or previously existing human, by growing *cloned* tissue from that individual. The term is generally used to refer to artificial human cloning; human clones in the form of identical twins are commonplace, with their cloning occurring during the natural process of reproduction.

Human cloning is amongst the most controversial forms of the practice. There have been numerous demands for all progress in the human cloning fields to be halted. One of the most ethically questionable problems with human cloning is farming of organs from clones. For

example, many believe it is unethical to use a human clone to save the life of another. In this scenario, the cloned human would be euthanized so that the vital organs could be harvested. This process of renewing the body's organs would potentially increase the life expectancy of a human by 50 years.

The cloning described above is reproductive cloning, not to be confused with research cloning in which only parts (such as an organ) are cloned using genetic material from a patient's tissues.

Ethical issues of human cloning

Roman Catholicism and many conservative Christian groups have opposed human cloning and the cloning of human embryos, believing that a human life begins the moment a human egg becomes fertilized. Other Christian denominations such as the United Church of Christ do not believe a fertilized egg constitutes a living being, but still they oppose the cloning of embryonic cells. The World Council of Churches, representing nearly 400 denominations worldwide, opposed cloning of both human embryos and whole humans in February 2006. The United Methodist Church opposed research and reproductive cloning in May 2000 and again in May 2004.

Libertarian views on the subject suggest that the federal government of the United States does not have the power to regulate cloning, as it is not given any such authority by the US constitution. (Similar to abortion rights.)

At present, the main objection to human cloning is that the cloned individual may be biologically damaged, due to the inherent unreliability of its origin: researchers currently are unable to safely and reliably clone non-human primates.

However, many believe that as cloning research and methods improve, concerns of safety and reliability will no longer be an issue. However, it must be pointed out that this has yet to occur, and may never occur. Rudolph Jaenisch, a professor at Harvard, has pointed out that we have become more efficient at producing clones which are still defective (Development Dynamics. Volume 235, pages 2460-2469. 2006). Other arguments against cloning come from various religious orders (believing cloning violates God's will or the natural order of life), and a general discomfort some have with the idea of "meddling" with the creation and basic function of life. This unease often manifests itself in contemporary novels, movies, and popular culture, much like numerous other scientific discoveries and inventions before. Various fictional scenarios portray clones being unhappy, soulless, or unable to integrate into society. Furthermore, clones are often depicted not as unique individuals but as "spare parts," providing organs for the clone's original (or any non-clone that requires replacement organs).

Needless to say, cloning is a poignant and important topic, reflected by its frequent discussion and debate among politicians, scientists, the media, religions, and the general public.

Cloning extinct and endangered species

Cloning, or more precisely, the reconstruction of functional DNA from extinct species has, for decades, been a dream of some scientists. The possible implications of this were dramatized in the best-selling novel by Michael Crichton and high budget Hollywood thriller Jurassic Park. In real life, one of the most anticipated targets for cloning was once the Woolly mammoth, but attempts to extract DNA from frozen mammoths have been unsuccessful, though a joint Russo-Japanese team is currently working toward this goal.[5]

In 2000, a cow named Bessie gave birth to a cloned Asian gaur, an endangered species, but the calf died after two days. In 2003, a banteng was successfully cloned, followed by three African wildcats from a thawed frozen embryo. These successes provided hope that similar techniques (using surrogate mothers of another species) might be used to clone extinct species. Anticipating this possibility, tissue samples from the last bucardo (Pyrenean Ibex) were frozen immediately after it died. Researchers are also considering cloning endangered species such as the giant panda, ocelot, and cheetah. The "Frozen Zoo" at the San Diego Zoo now stores frozen tissue from the world's rarest and most endangered species.[6][7]

In 2002, geneticists at the Australian Museum announced that they had replicated DNA of the Thylacine (Tasmanian Tiger), extinct about 65 years previous, using polymerase chain reaction.[8] However, on 2005-02-15 the museum announced that it was stopping the project after tests showed the specimens' DNA had been too badly degraded by the (ethanol) preservative. Most recently, on 2005-05-15, it was announced that the Thylacine project would be revived, with new participation from researchers in New South Wales and Victoria.

One of the continuing obstacles in the attempt to clone extinct species is the need for nearly perfect DNA. Cloning from a single specimen could not create a viable breeding population in sexually reproducing animals. Furthermore, even if males and females were cloned, the question would remain open if they would be viable at all in the absence of parents that could teach or show them natural behavior. Essentially, if cloning an extinct species succeeded — it must be considered that cloning still is an experimental technology that succeeds only by chance — it is far more likely than not that any resulting animals, even if they were healthy, would be little more than curios or museum pieces.

Cloning endangered species is a highly ideological issue. Many conservation biologists and environmentalists vehemently oppose cloning endangered species — not because they think it won't work but because they think it may deter donations to help preserve natural habitat and wild animal populations. The "rule-of-thumb" in animal conservation is that, if it is still feasible to conserve habitat and viable wild populations, breeding in captivity should not be undertaken in isolation.

In a 2006 review, David Ehrenfeld concludes that cloning in animal conservation is an experimental technology that, at its present state, cannot be expected to work except by pure chance and utterly fails a cost-benefit analysis.[9] Furthermore, he says, it is likely to siphon funds from established and working projects and does not address any of the issues underlying animal extinction (such as habitat destruction, hunting or other overexploitation, and an impoverished gene pool). While cloning technologies are well-established and used on a regular basis in plant conservation, care must be taken to ensure genetic diversity. He concludes:

"Vertebrate cloning poses little risk to the environment, but it can consume scarce conservation resources, and its chances of success in preserving species seem poor. To date, the conservation benefits of transgenics and vertebrate cloning remain entirely theoretical, but many of the risks are known and documented. Conservation biologists should devote their research and energies to the established methods of conservation, none of which require transgenics or vertebrate cloning.[9]"

Embryo

Somatic cell nuclear transfer can also be used to create a clonal embryo. The most likely scenario for this is to produce embryos for use in research, particularly stem cell research. This process is also called "research cloning" or "therapeutic cloning."

Therapeutic cloning, also called "embryo cloning," is the production of human embryos for use in research. The goal of this process is not to create cloned human beings, but rather to harvest stem cells that can be used to study human development and to treat disease. Stem cells are important to biomedical researchers because they can be used to generate virtually any type of specialized cell in the human body. Stem cells are extracted from the egg after it has divided for 5 days. The egg at this stage of development is called a blastocyst. The extraction process destroys the embryo, which raises a variety of ethical concerns. Many researchers hope that one day stem cells can be used to serve as replacement cells to treat heart disease, Alzheimer's, cancer, and other diseases.

Scientists believe that cloning may be used to create stem cells genetically compatible with the somatic cell donor. Cloning in stem cell research, called research cloning or therapeutic cloning, has not yet been successful: no embryonic stem cell lines have been derived from clonal embryos. The process might provide a way to grow organs in host carrier, which become completely compatible with the original. Host carrier growing poses a risk of trans-species diseases if the host is of a different species (e.g., a pig).

In human beings, this is a highly controversial issue for several reasons. It involves creating human embryos in vitro and then destroying them, attempting to obtain embryonic stem cells. But proposals to use cloning techniques in human stem cell research raise a set of concerns beyond the moral status of the embryo. These have led a number of individuals and organizations who are not opposed to human embryonic stem cell research to be concerned about, or opposed to, human research cloning. One concern is that cloning in human stem cell research will lead to the reproductive cloning of humans. A second concern is the appropriate sourcing of the eggs that are needed. Research cloning requires a large number of human eggs, which can only be obtained from women. A third concern is the feasibility of developing stem cell therapies from cloning.

In November 2001, scientists from Advanced Cell Technologies (ACT), a biotechnology company in Massachusetts, announced that they had cloned the first human embryos for the purpose of advancing therapeutic research. To do this, they collected eggs from women's ovaries and then removed the genetic material from these eggs with a needle less than 2/10,000th of an inch wide. A skin cell was inserted inside the enucleated egg to serve as a new nucleus. The egg began to divide after it was stimulated with a chemical called ionomycin. The results were limited in success. Although this process was carried out with

eight eggs, only three began dividing, and only one was able to divide into six cells before stopping.

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Genetic engineering

Genetic engineering, *genetic modification* (*GM*) and *gene splicing* are terms for the process of manipulating genes, usually outside the organism's normal reproductive process.

It involves the isolation, manipulation and reintroduction of DNA into cells or model organisms, usually to express a protein. The aim is to introduce new characteristics or attributes physiologically or physically, such as making a crop resistant to a herbicide, introducing a novel trait, or producing a new protein or enzyme. Examples can include the production of human insulin through the use of modified bacteria, the production of erythropoietin in Chinese Hamster Ovary cells, and the production of new types of experimental mice such as the OncoMouse (cancer mouse) for research, through genetic redesign.

Since a protein is specified by a segment of DNA called a gene, future versions of that protein can be modified by changing the gene's underlying DNA. One way to do this is to isolate the piece of DNA containing the gene, precisely cut the gene out, and then reintroduce (splice) the gene into a different DNA segment. Daniel Nathans and Hamilton Smith received

the 1978 Nobel Prize in physiology or medicine for their isolation of restriction endonucleases, which are able to cut DNA at specific sites. Together with ligase, which can join fragments of DNA together, restriction enzymes formed the initial basis of recombinant DNA technology.

Applications

The first Genetically Engineered drug was human insulin approved by the USA's FDA in 1982. Another early application of genetic engineering was to create human growth hormone as replacement for a drug that was previously extracted from human cadavers. In 1986 the FDA approved the first genetically engineered vaccine for humans, for hepatitis B. Since these early uses of the technology in medicine, the use of GE has expanded to supply many drugs and vaccines.

One of the best known applications of genetic engineering is that you can probilize the outcome of offspring. There are potentially momentous biotechnological applications of GM, for example oral vaccines produced naturally in fruit, at very low cost.

A radical ambition of some groups is human enhancement via genetics, eventually by molecular engineering.

Genetic engineering and research

Although there has been a tremendous revolution in the biological sciences in the past twenty years, there is still a great deal that remains to be discovered. The completion of the sequencing of the human genome, as well as the genomes of most agriculturally and scientifically important plants and animals, has increased the possibilities of genetic research immeasurably. Expedient and inexpensive access to comprehensive genetic data has become a reality with billions of sequenced nucleotides already online and annotated. Now that the rapid sequencing of arbitrarily large genomes has become a simple, if not trivial affair, a much greater challenge will be elucidating function of the extraordinarily complex web of interacting proteins, dubbed the proteome, that constitutes and powers all living things. Genetic engineering has become the gold standard in protein research, and major research progress has been made using a wide variety of techniques, including:

- Loss of function, such as in a knockout experiment, in which an organism is engineered to lack the activity of one or more genes. This allows the experimenter to analyze the defects caused by this mutation, and can be considerably useful in unearthing the function of a gene. It is used especially frequently in developmental biology. A knockout experiment involves the creation and manipulation of a DNA construct in vitro, which, in a simple knockout, consists of a copy of the desired gene which has been slightly altered such as to cripple its function. The construct is then taken up by embryonic stem cells, where the engineered copy of the gene replaces the organism's own gene. These stem cells are injected into blastocysts, which are implanted into surrogate mothers. Another method, useful in organisms such as Drosophila (fruit fly), is to

induce mutations in a large population and then screen the progeny for the desired mutation. A similar process can be used in both plants and prokaryotes.

- Gain of function experiments, the logical counterpart of knockouts. These are sometimes performed in conjunction with knockout experiments to more finely establish the function of the desired gene. The process is much the same as that in knockout engineering, except that the construct is designed to increase the function of the gene, usually by providing extra copies of the gene or inducing synthesis of the protein more frequently.
- 'Tracking' experiments, which seek to gain information about the localization and interaction of the desired protein. One way to do this is to replace the wild-type gene with a 'fusion' gene, which is a juxtaposition of the wild-type gene with a reporting element such as Green Fluorescent Protein (GFP) that will allow easy visualization of the products of the genetic modification. While this is a useful technique, the manipulation can destroy the function of the gene, creating secondary effects and possibly calling into question the results of the experiment. More sophisticated techniques are now in development that can track protein products without mitigating their function, such as the addition of small sequences which will serve as binding motifs to monoclonal antibodies.

Molecular genetics

Molecular genetics is the field of biology which studies the structure and function of genes at a molecular level. Molecular genetics employs the methods of genetics and molecular biology. It is so-called to differentiate it from other sub fields of genetics such as ecological genetics and population genetics. An important area within molecular genetics is the use of molecular information to determine the patterns of descent, and therefore the correct scientific classification of organisms: this is called molecular systematics.

Forward genetics

One of the first tools available to molecular geneticists is the forward genetic screen. The aim of this technique is to identify mutations that produce a certain phenotype. A mutagen is very often used to accelerate this process. Once mutants have been isolated, the mutated gene can be molecularly identified.

Reverse genetics

While forward genetic screens are productive, a more straightforward approach would be to determine the phenotype that results from mutating a given gene. This is called reverse genetics. In some organisms, such as yeast and mice, it is possible to induce the deletion of a particular gene, creating a gene knockout. Alternatives include the random induction of DNA deletions and subsequent selection for deletions in a gene of interest, the application of RNA interference and the creation of transgenic organisms that do not express a gene of interest.

See also

- The study of macromolecules important in biological inheritance
- Forward and reverse genetics screens
  - RNA interference
  - Gene knockout
- Transgenics and overexpression
- Mapping, cloning, and sequencing

- Gene expression
  - Measuring
  - Spatial and temporal regulation
  - cDNAs
- Imprinting
- Bacterial and phage molecular genetics
- Eukaryotic molecular genetics

DNA repair

DNA repair refers to a collection of processes by which a cell identifies and corrects damage to the DNA molecules that encode its genome. In human cells, both normal metabolic activities and environmental factors such as UV light can cause DNA damage, resulting in as many as 1 million individual molecular lesions per cell per day.[1] Many of these lesions cause structural damage to the DNA molecule and can alter or eliminate the cell's ability to transcribe the gene that the affected DNA encodes. Other lesions induce potentially harmful mutations in the cell's genome, which affect the survival of its daughter cells after it undergoes mitosis. Consequently, the DNA repair process must be constantly active so it can respond rapidly to any damage in the DNA structure.

The rate of DNA repair is dependent on many factors, including the cell type, the age of the cell, and the extracellular environment. A cell that has accumulated a large amount of DNA damage, or one that no longer effectively repairs damage incurred by its DNA, can enter one of three possible states:

1. an irreversible state of dormancy, known as senescence
2. cell suicide, also known as apoptosis or programmed cell death
3. unregulated cell division, which can lead to the formation of a tumor that is cancerous

The DNA repair ability of a cell is vital to the integrity of its genome and thus to its normal functioning and that of the organism. Many genes that were initially shown to influence lifespan have turned out to be involved in DNA damage repair and protection.[2] Failure to correct molecular lesions in cells that form gametes can introduce mutations into the genomes of the offspring and thus influence the rate of evolution.

DNA damage

DNA damage, due to environmental factors and normal metabolic processes inside the cell, occurs at a rate of 1,000 to 1,000,000 molecular lesions per cell per day.[1] While this constitutes only 0.000165% of the human genome's approximately 6 billion bases (3 billion base pairs), unrepaired lesions in critical genes (such as tumor suppressor genes) can impede a cell's ability to carry out its function and appreciably increase the likelihood of tumor formation.

The vast majority of DNA damage affects the primary structure of the double helix; that is, the bases themselves are chemically modified. These modifications can in turn disrupt the molecules' regular helical structure by introducing non-native chemical bonds or bulky adducts that do not fit in the standard double helix. Unlike proteins and RNA, DNA usually lacks secondary structure and therefore damage or disturbance does not occur at that level. DNA is, however, supercoiled and wound around "packaging" proteins called histones, and both superstructures are vulnerable to the effects of DNA damage.

Sources of damage

DNA damage can be subdivided into two main types:

1. endogenous damage such as attack by reactive oxygen species produced from normal metabolic byproducts (spontaneous mutation), especially the process of oxidative deamination;
2. exogenous damage caused by external agents such as
   - ultraviolet [UV 200-300nm] radiation from the sun
   - other radiation frequencies, including x-rays and gamma rays
   - hydrolysis or thermal disruption
   - certain plant toxins
   - human-made mutagenic chemicals, especially aromatic compounds that act as DNA intercalating agents
   - cancer chemotherapy and radiotherapy

The replication of damaged DNA before cell division can lead to the incorporation of wrong bases opposite damaged ones. Daughter cells that inherit these wrong bases carry mutations from which the original DNA sequence is unrecoverable (except in the rare case of a back mutation, for example, through gene conversion).

Types of damage

There are four main types of damage to DNA due to endogenous cellular processes:

- oxidation of bases [e.g. 8-oxo-7,8-dihydroguanine (8-oxoG)] and generation of DNA strand interruptions from reactive oxygen species,
- alkylation of bases (usually methylation), such as formation of 7-methylguanine
- hydrolysis of bases, such as deamination, depurination and depyrimidination.
- mismatch of bases, due to DNA replication in which the wrong DNA base is stitched into place in a newly forming DNA strand.

Damage caused by exogenous agents comes in many forms. Some examples are:

- UV light causes crosslinking between adjacent cytosine and thymine bases creating pyrimidine dimers
- Ionizing radiation such as that created by radioactive decay or in cosmic rays causes breaks in DNA strands
- Industrial chemicals such as vinyl chloride and hydrogen peroxide, and environmental chemicals such as polycyclic hydrocarbons found in smoke, soot and tar create a huge diversity of DNA adducts- ethenobases, oxidized bases and alkylated phosphotriesters, just to name a few.

Nuclear versus mitochondrial DNA damage

In human, and eukaryotic cells in general, DNA is found in two cellular locations - inside the nucleus and inside the mitochondria. Nuclear DNA (nDNA) exists as chromatin during non-replicative stages of the cell cycle and is condensed into aggregate structures known as chromosomes during cell division. In either state the DNA is highly compacted and wound up around bead-like proteins called histones. Whenever a cell needs to express the genetic information encoded in its nDNA the required chromosomal region is unravelled, genes located therein are expressed, and then the region is condensed back to its resting conformation. Mitochondrial DNA (mtDNA) is located inside mitochondria organelles, exists in multiple copies, and is also tightly associated with a number of proteins to form a complex known as the nucleoid. Inside mitochondria, reactive oxygen species (ROS), or free radicals, byproducts of the constant production of adenosine triphosphate (ATP) via oxidative phosphorylation, create a highly oxidative environment that is known to damage mtDNA. A critical enzyme in counteracting the toxicity of these species is superoxide dismutase, which is present in both the mitochondria and cytoplasm of eukaryotic cells.

Senescence and apoptosis

Senescence, an irreversible state in which the cell no longer divides (mitosis), is a protective response to the shortening of the chromosome ends (telomeres). The telomeres are long regions of repetitive noncoding DNA that cap chromosomes and undergo partial degradation each time a cell undergoes division (see Hayflick limit).[3] In contrast, quiescence is a reversible state of cellular dormancy that is unrelated to genome damage (see cell cycle). Senescence in cells may serve as a functional alternative to apoptosis in cases where the physical presence of a cell for spatial reasons is required by the organism,[4] which serves as a "last resort" mechanism to prevent a cell with damaged DNA from replicating inappropriately in the absence of pro-growth cellular signaling. Unregulated cell division can lead to the formation of a tumor (see cancer), which is potentially lethal to an organism. Therefore the induction of senescence and apoptosis is considered to be part of a strategy of protection against cancer.

DNA repair mechanisms

Cells cannot function if DNA damage corrupts the integrity and accessibility of essential information in the genome (but cells remain superficially functional when so-called "non-essential" genes are missing or damaged). Depending on the type of damage inflicted on the DNA's double helical structure, a variety of repair strategies have evolved to restore lost information. If possible, cells use the unmodified complementary strand of the DNA or the sister chromatid as a template to losslessly recover the original information. Without access to a template, cells use an error-prone recovery mechanism known as translesion synthesis as a last resort.

Damage to DNA alters the spatial configuration of the helix and such alterations can be detected by the cell. Once damage is localized, specific DNA repair molecules are summoned to, and bind at or near the site of damage, inducing other molecules to bind and form a complex that enables the actual repair to take place. The types of molecules involved and the mechanism of repair that is mobilized depend on the type of damage that has occurred and the phase of the cell cycle that the cell is in.

Direct reversal

Cells are known to eliminate three types of damage to their DNA by chemically reversing it. These mechanisms do not require a template, since the types of damage they counteract can only occur in one of the four bases. Such direct reversal mechanisms are specific to the type of damage incurred. The formation of thymine dimers (a common type of cyclobutyl dimer) upon irradiation with UV light results in an abnormal covalent bond between adjacent thymidine bases. The photoreactivation process in bacteria directly reverses this damage by the action of the enzyme photolyase, which uses energy absorbed from UV light to promote catalysis. Another type of damage, methylation of guanine bases, is directly reversed by the protein methyl guanine methyl transferase (MGMT). This is an expensive process because each MGMT molecule can only be used once; that is, the reaction is stoichiometric rather than catalytic.[5] A generalized response to methylating agents in bacteria is known as the adaptive response and confers a level of resistance to alkylating agents upon sustained exposure.[6]The third type of DNA damage reversed by cells is certain methylation of the bases cytosine and adenine.

Single strand damage

When only one of the two strands of a double helix has a defect, the other strand can be used as a template to guide the correction of the damaged strand. In order to repair damage to one of the two paired molecules of DNA, there exist a number of excision repair mechanisms that remove the damaged nucleotide and replace it with an undamaged nucleotide complementary to that found in the undamaged DNA strand.[5]

- Base excision repair (BER), which repairs damage due to a single nucleotide caused by oxidation, alkylation, hydrolysis, or deamination;
 Nucleotide excision repair (NER), which repairs damage affecting longer strands of 2-30 bases. This process recognizes bulky, helix-distorting changes such as thymine dimers as well as single-strand breaks (repaired with enzymes

such UvrABC endonuclease). A specialized form of NER known as Transcription-Coupled Repair (TCR) deploys high-priority NER repair enzymes to genes that are being actively transcribed;

Mismatch repair (MMR), which corrects errors of DNA replication and recombination that result in mispaired nucleotides following DNA replication.

Double strand breaks

A type of DNA damage particularly hazardous to dividing cells is a break to both strands in the double-helix. Two mechanisms exist to repair this damage. They are generally known as non-homologous end-joining (NHEJ) and recombinational repair (also known as template-assisted repair or homologous recombination repair).[5]

The NHEJ pathway operates when the cell has not yet replicated the region of DNA on which the lesion has occurred. The process directly joins the two ends of the broken DNA strands without a template, losing sequence information in the process. Thus this repair mechanism is necessarily mutagenic. However, if the cell is not dividing and has not replicated its DNA, the NHEJ pathway is the cell's only option. NHEJ relies on chance pairings, or microhomologies, between the single-stranded tails of the two DNA fragments to be joined. There are multiple independent "failsafe" pathways for NHEJ in higher eukaryotes.[7]

Recombinational repair requires the presence of an identical or nearly identical sequence to be used as a template for repair of the break. The enzymatic machinery responsible for this repair process is nearly identical to the machinery responsible for chromosomal crossover during meiosis. This pathway allows a damaged chromosome to be repaired using the newly created sister chromatid as a template, i.e. an identical copy that is also linked to the damaged region via the centromere. Double-stranded breaks repaired by this mechanism are usually caused by the replication machinery attempting to synthesize across a single-strand break or unrepaired lesion, both of which result in collapse of the replication fork.

It should be noted that topoisomerases sometimes introduce both single and double strand breaks in the course of changing the DNA's state of supercoiling, which is especially common in regions near an open replication fork. Such breaks are not considered DNA damage because they serve a biochemical purpose and are immediately repaired by the enzymes that created them.

A team of French researchers bombarded Deinococcus radiodurans to study the mechanism of double-strand break DNA repair in that organism. At least two copies of the genome, with random DNA breaks, can form DNA fragments through annealing. Partially overlapping fragments are then used for synthesis of homologous regions through a moving D-loop that can continue extension until they find complementary partner strands. In the final step there is crossover by means of RecA-dependent homologous recombination[8].

Translesion synthesis

Translesion synthesis is an error-prone (almost error-guaranteeing) last-resort method of repairing a DNA lesion that has not been repaired by any other mechanism. The DNA

replication machinery cannot continue replicating past a site of DNA damage, so the advancing replication fork will stall on encountering a damaged base. The translesion synthesis pathway is mediated by specific DNA polymerases that insert extra bases at the site of damage and thus allow replication to bypass the damaged base to continue with chromosome duplication. From the cell's perspective, it is "better" to introduce mutations around a single site than to continue the cell cycle with an incompletely replicated chromosome. The bases inserted by the translesion synthesis machinery are template-independent, but not arbitrary; for example, one human polymerase inserts adenine bases when synthesizing past a thymine dimer.[5]

DNA repair and aging

Poor DNA repair induces pathology

Experimental animals with genetic deficiencies in DNA repair often show decreased lifespan and increased cancer incidence. For example, mice deficient in the dominant NHEJ pathway and in telomere maintenance mechanisms get lymphoma and infections more often, and consequently have shorter lifespans than wild-type mice.[9] Similarly, mice deficient in a key repair and transcription protein that unwinds DNA helices have premature onset of aging-related diseases and consequent shortening of lifespan.[10] However, not every DNA repair deficiency creates exactly the predicted effects; mice deficient in the NER pathway exhibited shortened lifespan without correspondingly higher rates of mutation.[11]

If the rate of DNA damage exceeds the capacity of the cell to repair it, the accumulation of errors can overwhelm the cell and result in early senescence, apoptosis or cancer. Inherited diseases associated with faulty DNA repair functioning result in premature aging, increased sensitivity to carcinogens, and correspondingly increased cancer risk (see below). On the other hand, organisms with enhanced DNA repair systems, such as Deinococcus radiodurans, the most radiation-resistant known organism, exhibit remarkable resistance to the double strand break-inducing effects of radioactivity, likely due to enhanced efficiency of DNA repair and especially NHEJ.[12] It is noteworthy that some workers suguest that if a DNA damage event occurs during the self repair process then the combination of the two events will exert an effect greater than the sum of the individual events (if they occured with a long time delay between them), this is the basis of the second event theory favoured by C. Busby (The Low Level Radiation Campaign).

Longevity and caloric restriction

A number of individual genes have been identified as influencing variations in lifespan within a population of organisms. The effects of these genes is strongly dependent on the environment, particularly on the organism's diet. Caloric restriction reproducibly results in extended lifespan in a variety of organisms, likely via nutrient sensing pathways and decreased metabolic rate. The molecular mechanisms by which such restriction results in lengthened lifespan are as yet unclear (see [13] for some discussion); however, the behavior

of many genes known to be involved in DNA repair is altered under conditions of caloric restriction.

For example, increasing the gene dosage of the gene SIR-2, which regulates DNA packaging in the nematode worm Caenorhabditis elegans, can significantly extend lifespan.[14] The mammalian homolog of SIR-2 is known to induce downstream DNA repair factors involved in NHEJ, an activity that is especially promoted under conditions of caloric restriction.[15] Caloric restriction has been closely linked to the rate of base excision repair in the nuclear DNA of rodents,[16] although similar effects have not been observed in mitochondrial DNA.[17]

Interestingly, the C. elegans gene AGE-1, an upstream effector of DNA repair pathways, confers dramatically extended lifespan under free-feeding conditions but leads to a decrease in reproductive fitness under conditions of caloric restriction.[18] This observation supports the pleiotropy theory of the biological origins of aging, which suggests that genes conferring a large survival advantage early in life will be selected for even if they carry a corresponding disadvantage late in life.

Medicine and DNA repair modulation

Hereditary DNA repair disorders

Defects in the NER mechanism are responsible for several genetic disorders, including:

- xeroderma pigmentosum: hypersensitivity to sunlight/UV, resulting in increased skin cancer incidence and premature aging
- Cockayne syndrome: hypersensitivity to UV and chemical agents
- trichothiodystrophy: sensitive skin, brittle hair and nails

Mental retardation often accompanies the latter two disorders, suggesting increased vulnerability of developmental neurons.

Other DNA repair disorders include:

- Werner's syndrome: premature aging and retarded growth
- Bloom's syndrome: sunlight hypersensitivity, high incidence of malignancies (especially leukemias).
- ataxia telangiectasia: sensitivity to ionizing radiation and some chemical agents

All of the above diseases are often called "segmental progerias" ("accelerated aging diseases") because their victims appear elderly and suffer from aging-related diseases at an abnormally young age.

Other diseases associated with reduced DNA repair function include Fanconi's anemia, hereditary breast cancer and hereditary colon cancer.

DNA repair and cancer

Inherited mutations that affect DNA repair genes are strongly associated with high cancer risks in humans. Hereditary nonpolyposis colorectal cancer (HNPCC) is strongly associated with specific mutations in the DNA mismatch repair pathway. BRCA1 and BRCA2, two famous mutations conferring a hugely increased risk of breast cancer on carriers, are

both associated with a large number of DNA repair pathways, especially NHEJ and homologous recombination.

Cancer therapy procedures such as chemotherapy and radiotherapy work by overwhelming the capacity of the cell to repair DNA damage, resulting in cell death. Cells that are most rapidly dividing - most typically cancer cells - are preferentially affected. The side effect is that other non-cancerous but rapidly dividing cells such as stem cells in the bone marrow are also affected. Modern cancer treatments attempt to localize the DNA damage to cells and tissues only associated with cancer, either by physical means (concentrating the therapeutic agent in the region of the tumor) or by biochemical means (exploiting a feature unique to cancer cells in the body).

DNA repair and evolution

An Ancient and Conserved Mechanism

The basic processes of DNA repair are highly conserved among both prokaryotes and eukaryotes and even among bacteriophage (viruses that infect bacteria); however, more complex organisms with more complex genomes have correspondingly more complex repair mechanisms.[19] The ability of a large number of protein structural motifs to catalyze relevant chemical reactions has played a significant role in the elaboration of repair mechanisms during evolution. For an extremely detailed review of hypotheses relating to the evolution of DNA repair, see [20].

The fossil record indicates that single celled life began to proliferate on the planet at some point during the Precambrian period, although exactly when recognizably modern life first emerged is unclear. Nucleic acids became the sole and universal means of encoding genetic information, requiring DNA repair mechanisms that in their basic form have been inherited by all extant life forms from their common ancestor. The emergence of Earth's oxygen-rich atmosphere (known as the "oxygen catastrophe") due to photosynthetic organisms, as well as the presence of potentially damaging free radicals in the cell due to oxidative phosphorylation, necessitated the evolution of DNA repair mechanisms that act specifically to counter the types of damage induced by oxidative stress.

Evolutionary rate as a function of DNA repair rate

When DNA damage is not repaired properly, or is repaired by an error-prone mechanism, mutations are introduced into the genomes of the cell's progeny. When this occurs in a germ line cell that will eventually produce a gamete, the mutation is passed on to the affected organism's offspring. The rate of evolution in a particular species (or, more narrowly, in a particular gene) is a function of the rate of mutation and thus of the accuracy and the rate of the DNA repair pathway and factors that can influence it.[21]

See also

- DNA replication

- Gene therapy

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DNA replication

DNA replication or *DNA synthesis*, it is the process of copying a double-stranded DNA strand. Since DNA strands are antiparallel and complementary, each strand can serve as a template for the reproduction of the opposite strand. The template strand is preserved as a whole piece and the new strand is assembled from nucleotide triphosphates. This process is called semiconservative replication. Ideally, the two resulting strands are identical, although in reality there are always errors, though proofreading and error-checking mechanisms exist to ensure a very high level of fidelity.

In a cell, this step is obligatory prior to cell division. Prokaryotes persistently replicate their DNA and creating a whole, new chromosome is a limiting step in cell division. In eukaryotes, timings are highly regulated and this occurs during the S phase of the cell cycle, preceding mitosis or meiosis I. The process may also be performed in vitro using reconstituted or completely artificial components, in a process known as PCR.

DNA may be synthesized artificially, but this process is not fundamentally a replicative process, and only produces one strand of DNA.

Introduction

DNA replication or DNA synthesis, it is the process of copying a double-stranded DNA strand. Since DNA strands are antiparallel and complementary, each strand can serve as a

template for the reproduction of the opposite strand. The template strand is preserved as a whole piece and the new strand is assembled from nucleotide triphosphates. This process is called semiconservative replication. Ideally, the two resulting strands are identical, although in reality there are always errors, though proofreading and error-checking mechanisms exist to ensure a very high level of fidelity.

In a cell, this step is obligatory prior to cell division. Prokaryotes persistently replicate their DNA and creating a whole, new chromosome is a limiting step in cell division.The large size of eukaryotic chromosomes and the limits of nucleotide incorporation during DNA synthesis, make it necessary for multiple origins of replication to exist in order to complete replication in a reasonable period of time. However, it is clear that at a replication origin the strands of DNA must dissociate and unwind in order to allow access to DNA polymerase.

The process may also be performed in vitro using reconstituted or completely artificial components, in a process known as PCR. DNA may be synthesized artificially, but this process is not fundamentally a replicative process, and only produces one strand of DNA.

3 Steps for DNA polymerization

This is a description of DNA polymerization using an enzyme. This is not the synthetic, purely chemical, laboratory method of artificially synthesizing oligos in a laboratory or oligo factory. Artificially synthesized oligos are a key aspect of the Polymerase Chain Reaction (PCR).

Initiation

In the initiation step, several key factors are recruited to an origin of replication. This origin of replication is unwound (i.e., the two strands are pulled apart at that site) and the partially unwound strands form a "replication bubble", with one replication fork on either end. Each group of enzymes at the replication fork moves away from the origin, unwinding and replicating the original DNA strands as they proceed. Primers mark the individual sequences and the starting points to be replicated.

The factors involved are collectively called the pre-replication complex. It consists of the following:

- A topoisomerase, which introduces negative supercoils into the DNA in order to minimize tortional strain induced by the unwinding of the DNA by helicase ahead of the replicational complex. The topoisomerase reversibly breaks the DNA strand, allowing the DNA to swivel, preventing the DNA from knotting up.
- A helicase, which unwinds and splits the DNA ahead of the fork. Thereafter, single-strand binding proteins (SSB) swiftly bind to the separated DNA, preventing the strands from reuniting.
- A primase (DnaG or RNA polymerase in prokaryotes, DNA polymerase ± in eukaryotes), which generates an RNA primer to be used in DNA replication.

- A DNA holoenzyme, which in reality is a complex of proteins that together perform the "actual" replication, i.e., the polymerization of nucleotides complementary to the template strand.
  - DNA polymerase III in prokaryotes DNA polymerase ´ and DNA pol µ in eukaryotes.

Elongation

5' _ _ _ _ _ _ _ _ _ _ _3' <--DNA template Primer-DNA-Primer-DNA <--Okazaki fragments 3' _ _ _ _ _ _ _ _ _ _ _5' <--complimentary DNA strand

At the beginning of elongation, an enzyme called DNA polymerase binds to the DNA and synthesizes DNA from the RNA primer, which indicates the starting point for the elongation. DNA polymerases can only synthesize the new DNA in the 5' to 3' direction. Because of this these enzymes can only travel on one side of the original strand without any interruption. This new strand, which proceeds from 5' to 3', is the leading strand. The other new strand, which procedes from 3' to 5', is the lagging strand.

In prokaryotes RNA primers are removed by DNA polymerase I, which also synthesizes DNA in their place, in eukaryotes they are removed by RNase H or FER1 and replaced with DNA by DNA polymerase ´ or µ.

Since DNA synthesis only occurs in the 5' to 3' direction, the DNA of the lagging strand is replicated in pieces known as Okazaki Fragments. Each time DNA polymerase reaches the 5' end of the RNA primer for the next Okazaki fragment, it dissociates and reassociates at the 3' end of the primer. Another enzyme, DNA ligase, is necessary to connect the Okazaki fragments.

In prokaryotes, leading strand and lagging strand synthesis are coupled by the action of the DNA polymerase III holoenzyme. One complex replicates the leading and lagging strands simultaneously. During this stage helicase continues to unwind the DNA into two single strands while topoisomerases relieves the supercoiling caused by this.

Both prokaryotes and eukaryotes have DNA polymerases with proof-reading and 3' exonuclease activities. These functions increase the fidelity of replication. Prokaryotes tend to have fewer or weaker proof-reading mechanisms due to the nature of their natural selection of their gene pools.

Termination

Termination occurs when DNA replication forks meet one another or run to the end of a linear DNA molecule. Also, termination may occur when a replication fork is deliberately stopped by a special protein, called a replication terminator protein, that binds to specific sites on a DNA molecule.

When the polymerase reaches the end of a linear DNA molecule, there is a potential problem due to the antiparallel structure of DNA. Because an RNA primer must be regularly laid down on the lagging strand, the last section of the lagging-strand DNA cannot be

replicated because there is no DNA template for the primer to be synthesized on. To solve this problem, the ends of most chromosomes consist of noncoding DNA that contains repeat sequences. The end of a linear chromosome is called the telomere. Cells can endure the shortening of the chromosome at the telomere to a degree, since it's necessary for chromosome stability. Many cells use an enzyme called telomerase that adds the repeat units to the end of the chromosome so the ends do not become too short after multiple rounds of DNA replication. Many simple, single-celled organisms overcome the whole problem by having circular chromosomes.

Before the DNA replication is finally complete, enzymes are used to proofread the sequences to make sure the nucleotides are paired up correctly in a process called DNA repair. If mistake or damage occurs, enzymes such as a nuclease will remove the incorrect DNA. DNA polymerase will then fill in the gap.

Equation

A chemical equation can be written that represents the process:

$(DNA)_{\boldsymbol{n}}$ + dNTP ’ $(DNA)_{\boldsymbol{n+1}}$ + $PP_{\boldsymbol{i}}$

Nucleotides (dNTP) used by DNA replications contain three phosphates attached to the sugar, like ATP and are named accordingly CTP, TTP, and GTP. However, in contrast to most other processes of the cell in which only one phosphate group ($P_{\boldsymbol{i}}$), the last two phosphate groups ($PP_{\boldsymbol{i}}$) (pyrophosphate group) are detached.

Organization of multiple replication sites

A diploid human cell contains 6 billion nucleotide pairs (arrayed in 46 linear chromosomes) that are copied at about 50 base pairs per second by each replication fork. Yet in a typical cell the entire replication process takes only about 8 hours. This is because there are many replication origin sites on a eukaryotic chromosome. Therefore, replication can begin at some origins earlier than at others. As replication nears completion, "bubbles" of newly replicated DNA meet and fuse, forming two new molecules.

There must be some form of regulation and organization of these multiple replication sites to prevent conflict. To date, two replication control mechanisms have been identified: one positive and one negative. For DNA to be replicated, each replication origin site must be bound by a set of proteins called the origin recognition complex. These remain attached to the DNA throughout the replication process. Specific accessory proteins, called licensing factors, must also be present for initiation of replication. Destruction of these proteins after initiation of replication prevents further replication cycles from occurring. This is because licensing factors are only produced when the nuclear membrane of a cell breaks down during mitosis.

See also

- Immortal DNA strand hypothesis

DNA polymerase

A *DNA polymerase* is an enzyme that assists in DNA replication. Such enzymes catalyze the polymerization of deoxyribonucleotides alongside a DNA strand, which they "read" and use as a template. The newly-polymerized molecule is complementary to the template strand and identical to the template's partner strand.

All DNA polymerases synthesize DNA in the 5' to 3' direction. No known DNA polymerase is able to begin a new chain (de novo). They can only add a nucleotide onto a preexisting 3'-OH group. For this reason, DNA polymerase needs a primer at which it can add the first nucleotide. Primers consist of RNA and DNA bases with the first two bases always being RNA, and are synthesized by another enzyme called primase. An enzyme known as a helicase is required to unwind DNA from a double-strand structure to a single-strand structure to facilitate replication of each strand consistent with the semiconservative model of DNA replication.

DNA polymerases have highly-conserved structure, which means that their overall catalytic subunits vary, on a whole, very little from species to species. Conserved structures usually indicate evolutionary advantages. DNA polymerase is considered to be a holoenzyme since it requires a Magnesium ion as a co-factor to function properly. In the absence of the Magnesium ion, it is referred to as an apoenzyme.

Error correction is a property of some, but not all, DNA polymerases. This process corrects mistakes in newly-synthesized DNA. When an incorrect base pair is recognized, DNA polymerase reverses its direction by one base pair of DNA. The 3'->5' exonuclease activity of the enzyme allows the incorrect base pair to be excised (this activity is known as proofreading). Following base excision, the polymerase can re-insert the correct base and replication can continue.

Some viruses also encode special DNA polymerases which may selectively replicate viral DNA through a variety of mechanisms. Retroviruses encode an unusual DNA polymerase called reverse transcriptase, which is an RNA-dependent DNA polymerase (RdDp). It polymerizes DNA from a template of RNA.

DNA polymerase families

Based on sequence homology, DNA polymerases can be further subdivided into seven different families A, B, C, D, X, Y, and RT.

Family A

Family A polymerases contain both replicative and repair polymerases. Replicative members from this family include the extensively studied T7 DNA polymerase as well as the eukaryotic mitochondrial DNA Polymerase [3]. Among the repair polymerases are E. coli DNA pol I, Thermus aquaticus pol I, and Bacillus stearothermophilus pol I. These repair polymerases are involved in excision repair and processing of Okazaki fragments generated during lagging strand synthesis.

Family B

Family B polymerases mostly contain replicative polymerases and include the major eukaryotic DNA polymerases ±, ´, μ, and also DNA polymerase ¶. Family B also includes DNA polymerases encoded by some bacteria and bacteriophages, of which the best characterized are from T4, Phi29 and RB69 bacteriophages. These enzymes are involved in both leading and lagging strand synthesis. A hallmark of the B family of polymerases is remarkable accuracy during replication and many have strong 3'-5' exonuclease activity (except DNA polymerase ± and ¶ which have no proofreading activity).

Family C

Family C polymerases are the primary bacterial chromosomal replicative enzymes and thus have polymerase and 3'-5' exonuclease activity.

Family D

Family D polymerases are still not very well characterized. All known examples are found in the Euryarchaeota subdomain of Archaea and are thought to be replicative polymerases.

Families X

Family X contains the well known eukaryotic polymerase pol ² as well as other eukaryotic polymerases such as pol Ã, pol », pol ¼, and terminal deoxynucleotidyl transferase (TdT). Pol ² is required for short-patch base excision repair, a DNA repair pathway that is essential for repairing abasic sites. Pol » and Pol ¼ are involved in non-homologous end joining, a mechanism for rejoining DNA double-strand breaks. TdT is only expressed in lymphoid tissue and adds "n nucleotides" to double-strand breaks formed during V(D)J recombination to promote immunological diversity.

Families Y

The Y-family polymerases differ from others in having a low fidelity on undamaged templates and in their ability to replicate through damaged DNA. Members of this family are hence called translesion sythesis (TLS) polymerases. Depending on the lesion TLS polymerases can bypass the damage in an error-free or error-prone fashion, the latter resulting in elevated mutagenesis. Xeroderma pigmentosum variant (XPV) patients for instance have mutations in the gene encoding Pol · (eta), which is error-free for UV-lesions. In XPV patients alternative error-prone polymerases e.g. Pol¶ (zeta) (polymerase ¶ is a B Family polymerase), are thought to be involved in mistakes which result in the cancer predisposition of these patients. Other members in humans are Pol ¹ (iota), Pol º (kappa) and Rev1 (terminal deoxycytidyl transferase). In E.coli two TLS polymerases, Pol IV (DINB) and PolV (UMUC), are known.

Family RT

Finally, the reverse transcriptase family contain examples both from retroviruses and eukaryotic polymerases. The eukaryotic polymerases are usually restricted to telomerases. These polymerases use a RNA template to synthesize the DNA strand.

Prokaryotic DNA polymerases

Bacteria have 5 known DNA polymerases:

- *Pol I*: Is implicated in DNA repair and has both 5'->3'(Nick translation) and 3'->5' (Proofreading) exonuclease activity.
- *Pol II*: Pol II is involved in replication of damaged DNA and has both 5'->3'chain extension ability and 3'->5' exonuclease activity.
- *Pol III*: is the main polymerase in bacteria (elongates in DNA replication), as such it has 3'->5' exonuclease proofreading ability.
- *Pol IV*: is a Y-family DNA polymerase
- *Pol V*: is a Y-family DNA polymerase and participates in bypassing DNA damage

Eukaryotic DNA polymerases

Eukaryotes have at least 15 DNA Polymerases[1]:

- *Pol ±*: acts as a primase (synthesizing a RNA primer), and then as a DNA Pol elongating that primer with DNA nucleotides. After a few hundred nucleotides elongation is taken over by Pol ´ and µ.
- *Pol ²*: is implicated in repairing DNA.
- *Pol ³*: replicates mitochondrial DNA.
- *Pol ´*: is the main polymerase in eukaryotes, it is highly processive and has 3'->5' exonuclease activity.
- *Pol µ*: may substitute for *Pol ´* in lagging strand synthesis, however the exact role is uncertain.
- ·, ¹, º, and *Rev1* are Y-family DNA polymerases and *Pol ¶* is a B-family DNA polymerase. These polymerases are involved in the bypass of DNA damage.[2]
- There are also other eukaryotic polymerases known, which are not as well characterized: *¸*, *»*, *Æ*, *Ã*, and *¼*. There are also others, but the nomenclature has become quite jumbled. See the External Links or do a quick search of PubMed to get the most up-to-date information.

None of the eukariotic polymerases can remove primers (5'->3' exonuclease activity), that function is carried out by other enzymes. Only the polymerases that deal with the elongation (³, ´ and µ) have proofreading ability (3'->5' exonuclease).

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Gene expression

Gene expression, or simply *expression*, is the process by which a gene's DNA sequence is converted into the structures and functions of a cell. Non-protein coding genes (e.g. rRNA genes, tRNA genes) are not translated into protein.

Gene expression is a multi-step process that begins with transcription of DNA, which genes are made of, into messenger RNA. It is then followed by post transcriptional modification and translation into a gene product, followed by folding, post-translational modification and targeting. The amount of protein that a cell expresses depends on the tissue, the developmental stage of the organism and the metabolic or physiologic state of the cell.

Patterns of gene expression

Numerous terms are used to describe patterns of gene expression, including:

- A *constitutive gene* is a gene that is transcribed continually compared to a facultative gene which is only transcribed when needed.
- A *housekeeping gene* is typically a constitutive gene that is transcribed at a relatively constant level. The housekeeping gene's products are typically needed for maintenance of the cell. It is generally assumed that their expression is unaffected by experimental conditions. Examples include actin, GAPDH and ubiquitin.
- A *facultative gene* is a gene which is only transcribed when needed compared to a constitutive gene.
- An *inducible gene* is a gene whose expression is either responsive to environmental change or dependent on the position of the cell cycle.

Measurement

Indirectly, the expression of particular genes may be assessed with DNA microarray technology, which can provide a rough measure of the cellular concentration of different messenger RNAs; often thousands at a time. While the name of this type of assessment is actually a misnomer, it is often referred to as expression profiling. The expression of many genes is known to be regulated after transcription, so an increase in mRNA concentration need not always increase expression. A more sensitive and more accurate method of relative gene expression measurement is real-time polymerase chain reaction. With carefully constructed standard curve it can even produce an absolute measurement such as in number of copies of mRNA per nanolitre of homogenized tissue, or in number of copies of mRNA per total poly-adenosine RNA. Protein expression levels can be measured by fusing the desired protein to another reporter protein, such as the green fluorescent protein or the enzyme beta-galactosidase. The expression level of these reporter proteins can be directly quantified using standard techniques.

Regulation of gene expression

Regulation of gene expression is the cellular control of the amount and timing of appearance of the functional product of a gene. Any step of gene expression may be modulated, from the DNA-RNA transcription step to post-translational modification of a protein. Gene regulation gives the cell control over structure and function, and is the basis for cellular differentiation, morphogenesis and the versatility and adaptability of any organism.

Overexpression

The protein encoded for by a gene can be expressed in increased quantity. This can come about by increasing the number of copies of the gene or increasing the binding strength of the promoter region.

Often, the DNA sequence for a protein of interest will be cloned or subcloned into a plasmid containing the lac promoter, which is then transformed into the bacterium Escherichia coli. Addition of IPTG (a lactose analog) causes the bacteria to express the protein of interest. However, this strategy does not always yield functional protein, in which case, other organisms or tissue cultures may be more effective. As for example the yeast, Saccharomyces cerevisiae, is often preferred to bacteria for proteins that undergo extensive Posttranslational modification. Nonetheless, bacterial expression has the advantage of easily producing large amounts of protein, which is required for X-ray crystallography or nuclear magnetic resonance experiments for structure determination.

Gene networks and expression

Genes have sometimes been regarded as nodes in a network, with inputs being proteins such as transcription factors, and outputs being the level of gene expression. The node itself performs a function, and the operation of these functions have been interpreted as performing a kind of information processing within cell and determine cellular behaviour.

Techniques

- Primer: Used to facilitate expression
- Shuttle Vector

Posttranslational modification

Posttranslational modification is the chemical modification of a protein after its translation. It is one of the later steps in protein biosynthesis for many proteins.

A protein (also called a polypeptide) is a chain of amino acids. During protein synthesis, 20 different amino acids can be incorporated in proteins. After translation, the posttranslational modification (PTM) of amino acids extends the range of functions of the

protein by attaching to it other biochemical functional groups such as acetate, phosphate, various lipids and carbohydrates, by changing the chemical nature of an amino acid (e.g. citrullination) or by making structural changes, like the formation of disulfide bridges.

Also, enzymes may remove amino acids from the amino end of the protein, or cut the peptide chain in the middle. For instance, the peptide hormone insulin is cut twice after disulfide bonds are formed, and a propeptide is removed from the middle of the chain; the resulting protein consists of two polypeptide chains connected by disulfide bonds.

Other modifications, like phosphorylation, are part of common mechanisms for controlling the behavior of a protein, for instance activating or inactivating an enzyme.

PTMs involving addition of functional groups

PTMs involving addition include:

- acetylation, the addition of an acetyl group, usually at the N-terminus of the protein
- alkylation, the addition of an alkyl group (e.g. methyl, ethyl)
  - methylation the addition of a methyl group, usually at lysine or arginine residues. (This is a type of alkylation.)
- biotinylation, acylation of conserved lysine residues with a biotin appendage

glutamylation, covalent linkage of glutamic acid residues to tubulin and some other proteins.
glycylation, covalent linkage of one to more than 40 glycine residues to the tubulin C-terminal tail
glycosylation, the addition of a glycosyl group to either asparagine, hydroxylysine, serine, or threonine, resulting in a glycoprotein
isoprenylation, the addition of an isoprenoid group (e.g. farnesol and geranylgeraniol)
lipoylation, attachment of a lipoate functionality
phosphopantetheinylation, the addition of a 4'-phosphopantetheinyl moiety from coenzyme A, as in fatty acid, polyketide, non-ribosomal peptide and leucine biosynthesis
phosphorylation, the addition of a phosphate group, usually to serine, tyrosine, threonine or histidine
sulfation, the addition of a sulfate group to a tyrosine.
Selenation
C-terminal amidation

PTMs involving addition of other proteins or peptides

- ISGylation, the covalent linkage to the ISG15 protein (Interferon-Stimulated Gene 15) (2)

SUMOylation, the covalent linkage to the SUMO protein (Small Ubiquitin-related

MOdifier) (1)
ubiquitination, the covalent linkage to the protein ubiquitin.

PTMs involving changing the chemical nature of amino acids

- citrullination, or deimination the conversion of arginine to citrulline deamidation, the conversion of glutamine to glutamic acid or asparagine to aspartic acid

PTMs involving structural changes

- disulfide bridges, the covalent linkage of two cysteine amino acids proteolytic cleavage, cleavage of a protein at a peptide bond

Case examples

- cleavage and formation of disulfide bridges during the production of insulin
PTM of histones as regulation of transcription: RNA polymerase control by chromatin structure
PTM of RNA polymerase II as regulation of transcription: RNA polymerase II

Protease

Proteases (proteinases, peptidases, or proteolytic enzymes) are enzymes that break peptide bonds between amino acids of proteins. The process is called peptide cleavage, a common mechanism of activation or inactivation of enzymes, especially those involved in blood coagulation or digestion. They use a molecule of water for this and are thus classified as hydrolases.

Classification

There are currently six classes of proteases:

- Serine proteases
Threonine proteases
Cysteine proteases
Aspartic acid proteases (e. g., plasmepsin)
Metalloproteases
Glutamic acid proteases

the threonine and glutamic acid proteases were not described until 1995 and 2004, respectively. The mechanism used to cleave a peptide bond involves making an amino acid residue that has the character of a polarized peptide bond (serine, cysteine and threonine peptidases) or a water molecule (aspartic acid, metallo- and glutamic acid peptidases)

nucleophilic so that it can attack the peptide carbonyl group. One way to make a nucleophile is by a catalytic triad, where a histidine residue is used to activate serine, cysteine or threonine as a nucleophile.

Occurrence

Proteases occur naturally in all organisms and constitute 1-5% of the gene content. These enzymes are involved in a multitude of physiological reactions from simple digestion of food proteins to highly regulated cascades (e.g., the blood clotting cascade, the complement system, apoptosis pathways, and the invertebrate prophenoloxidase activating cascade). Peptidases can break either specific peptide bonds (limited proteolysis), depending on the amino acid sequence of a protein, or break down a complete peptide to amino acids (unlimited proteolysis). The activity can be a destructive change abolishing a protein's function or digesting it to its principal components; it can be an activation of a function or it can be a signal in a signalling pathway.

Inhibitors

The function of peptidases is inhibited by protease inhibitor enzymes. Examples of protease inhibitors are the class of serpins (serine protease or peptidase inhibitors), incorporating alpha 1-antitrypsin. Other serpins are complement 1-inhibitor, antithrombin, alpha 1-antichymotrypsin, plasminogen activator inhibitor 1 (coagulation, fibrinolysis) and the recently discovered neuroserpin.

The natural protease inhibitors are not to be confused with the protease inhibitors used in antiretroviral therapy. Some viruses, with HIV among them, depend on proteases in their reproductive cycle. Thus, protease inhibitors are developed as antiviral means.

Degradation

Proteases, being themselves proteins, are known to be cleaved by other protease molecules, sometimes of the same variety. This may be an important method of regulation of peptidase activity.

Protease research

The field of protease research is enormous. Barrett and Rawlings estimated that approximately 8000 papers related to this field are published each year.

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Ubiquitin

Ubiquitin is a small regulatory protein that is ubiquitous in eukaryotes. *Ubiquitination* (or *Ubiquitylation*) refers to the post-translational modification of a protein by the covalent attachment (via an isopeptide bond) of one or more ubiquitin monomers. Ubiquitin (originally, *Ubiquitous Immunopoietic Polypeptide*) was first identified in 1975 as an 8.5 kDa protein of unknown function expressed universally in living cells. The basic functions of ubiquitin and the components of the ubiquitination pathway were elucidated in the early 1980s in groundbreaking work performed by Aaron Ciechanover, Avram Hershko and Irwin Rose for which the Nobel Prize in Chemistry was awarded in 2004.

Poly-ubiquitination, the process in which a chain of at least four ubiquitin peptides are attached to a lysine on a substrate protein, most commonly results in the degradation of the substrate protein via the proteasome. Apparently, at least four ubiquitins are required on a substrate protein in order for the proteasome to bind and therefore degrade the substrate (though there are examples of non-ubiquitinated proteins being targeted to the proteasome).

Mono-ubiquitination, the process in which a single ubiquitin peptide is bound to a substrate, initiates cell signaling by allowing other proteins that contain ubiquitin binding domains to interact with the mono-ubiquitinated substrate. Mono-ubiquitination has been associated with targeting of membrane proteins to the lysosome, for example.

The ubiquitylation system was initially characterised as an ATP-dependent proteolytic system present in cellular extracts. A heat-stable polypeptide present in these extracts, ATP-dependent proteolysis factor 1 (APF-1), was found to become covalently attached to the model protein substrate lysozyme in an ATP and Mg2+-dependent process. Multiple APF-1 molecules were linked to a single substrate molecule by an isopeptide linkage and conjugates were found to be rapidly degraded with the release of free APF-1. Soon after APF-1-protein conjugation was characterised, APF-1 was identified as ubiquitin. The carboxyl group of the C-terminal glycine residue of ubiquitin (Gly76) was identified as the moiety conjugated to substrate lysine residues.

The protein

Ubiquitin properties (human)

Number of residues 76

Molecular mass 8564.47 Da

Isoelectric point (pI) 6.79

Gene names RPS27A (UBA80, UBCEP1), UBA52 (UBCEP2), UBB, UBC

Ubiquitin is a small protein that occurs in all eukaryotic cells. Its main function is to mark other proteins for destruction, known as proteolysis. Several ubiquitin molecules attach to the condemned protein (polyubiquitination), and it then moves to a proteasome, a barrel-shaped structure where the proteolysis occurs. Ubiquitin can also mark transmembrane proteins (for example, receptors) for removal from membranes and fulfill several signalling roles within the cell.

Ubiquitin consists of 76 amino acids and has a molecular mass of about 8500 Da. It is highly conserved among eukaryotic species: Human and yeast ubiquitin share 96 % sequence identity. The human ubiquitin sequence is:

MQIFVKTLTGKTITLEVEPSDTIENVKAKIQDKEGIPPDQQRLIFAGKQLEDGRTLSDYNIQKESTL
HLVLRLRGG

Ubiquitylation

The process of marking a protein with ubiquitin (ubiquitylation or ubiquitination) consists of a series of steps:

1. Activation of ubiquitin - Ubiquitin is activated in a two-step reaction by an E1 ubiquitin-activating enzyme in a process requiring ATP as an energy source. The initial step involves production of an ubiquitin-adenylate intermediate. The second step transfers ubiquitin to the E1 active site cysteine residue, with release of AMP. This step results in a thioester linkage between the C-terminal carboxyl group of ubiquitin and the E1 cysteine sulfhydryl group.
2. Transfer of ubiquitin from E1 to the active site cysteine of an ubiquitin-conjugating enzyme E2 via a trans(thio)esterification reaction. Mammalian genomes contain 20-30 UBCs.
3. The final step of the ubiquitylation cascade generally requires the activity of one of the hundreds of E3 ubiquitin-protein ligases (often termed simply ubiquitin ligase). E3 enzymes function as the substrate recognition modules of the system and are capable of interaction with both E2 and substrate. E3 enzymes possess one of two domains:
    - The *HECT* (Homologous to the E6-AP Carboxyl Terminus) domain
    - The *RING* domain (or the closely related *U-box* domain)

Transfer can occur in two ways:

- Directly from E2, catalysed by RING domain E3s.
- Via an E3 enzyme, catalysed by HECT domain E3s. In this case, a covalent E3-ubiquitin intermediate is formed before transfer of ubiquitin to the substrate protein.

In many cases, ubiquitin molecules are further added on to previously-conjugated ubiquitin molecules to form a polyubiquitin chain. If the chain is longer than 3 ubiquitin molecules, the tagged protein is rapidly degraded by the 26S-proteasome into small peptides (usually 3-24 amino acid residues in length). Ubiquitin moieties are cleaved off the protein by deubiquitinating enzymes and are recycled for further use.

Cell-surface transmembrane molecules that are tagged with ubiquitin are often mono-ubiquitinated, and this modification alters the subcellular localization of the protein, often targeting the protein for destruction in lysosomes.

The ubiquitin pathway is thought to be the method of cellular egress for a number of retroviruses, including HIV and Ebola, but the exact mechanism by which this occurs has yet to be deduced.

The Anaphase-promoting complex (APC) and the SCF complex (for Skp1-Cullin-F-box protein complex) are two examples of multi-subunit E3s involved in recognition and ubiquitination of specific target proteins for degradation by the proteasome.

Disease association

Genetic disorders

- The gene whose disruption causes Angelman syndrome, UBE3A, encodes an ubiquitin ligase (E3) enzyme termed E6-AP.
- The gene disrupted in Von Hippel-Lindau syndrome encodes an ubiquitin E3 ligase termed the VHL tumor suppressor or VHL gene.
- The gene disrupted in Liddle's Syndrome results in disregulation of an epithelial Na+ channel (ENaC) and causes hypertension.

Immunohistochemistry

Antibodies to ubiquitin are used in histology to identify abnormal accumulations of protein inside cells that are markers of disease. These accumulations are called inclusion bodies. Examples of such abnormal inclusions in cells are

- Neurofibrillary tangles in Alzheimer's disease

Lewy body in Parkinson's disease
Pick bodies in Pick's disease
Inclusions in motor neuron disease
Mallory's Hyalin in alcoholic liver disease
Rosenthal fibres in astrocytes

Further reading

- Essays in Biochemistry, Volume 41 (2005): The Ubiquitin-Proteasome System (Portland Press)

Protein biosynthesis

Within the nucleus of the cell (light blue), genes (DNA, dark blue) are transcribed into RNA. This RNA is then subject to post-transcriptional modification and control, resulting in a mature mRNA (red) that is then transported out of the nucleus and into the cytoplasm (peach), where it undergoes translation into a protein. mRNA is translated by ribosomes (purple) that match the three-base codons of the mRNA to the three-base anti-codons of the appropriate tRNA. Newly synthesized proteins (black) are often further modified, such as by binding to an effector molecule (orange), to become fully active.

Protein biosynthesis (Synthesis) is the process in which cells build proteins. The term is sometimes used to refer only to protein translation but more often it refers to a multi-step process, beginning with amino acid synthesis and transcription which are then used for translation. Protein biosynthesis, although very similar, differs between prokaryotes and eukaryotes.

Amino acid synthesis

Amino acids are the monomers which are polymerized to produce proteins. Amino acid synthesis is the set of biochemical processes (metabolic pathways) which build the amino acids from carbon sources like glucose. Not all amino acids may be synthesised by every organism, for example adult humans have to obtain 8 of the 20 amino acids from their diet.

The amino acids are then loaded onto tRNA molecules for use in the process of translation.

Transcription

Transcription is the process by which an mRNA template, carrying the sequence of the protein, is produced for the translation step from the genome. Transcription makes the template from one strand of the DNA double helix, called the template strand. Transcription takes place in 3 stages.

1. Transcription starts with the process of initiation. RNA polymerase, the enzyme which produced RNA from a DNA template, binds to a specific region on DNA that designates the starting point of transcription. This binding region is called the promoter. As the RNA polymerase binds on to the promoter, the DNA strands are beginning to unwind.
2. The second process is elongation. RNA polymerase travels along the template (noncoding) strand, synthesizing a ribonucleotide polymer. RNA

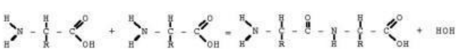
polymerase does not use the coding strand as a template because a copy of any strand produces a base sequence *complementary* to the strand which is being copied. Therefore DNA from the noncoding strand is used as a template to copy the coding strand.

3. The third stage is termination. As the polymerase reaches the termination stage, modifications are required for the newly transcribed mRNA to be able to travel to the other parts of the cell, including cytoplasm and endoplasmic reticulum for translation. A 5' cap is added to the mRNA to protect it from degradation. In eukaryotes a poly-A tail is added on the 3' end for protection and as a template for further process. Also in eukaryotes (higher organisms) the vital process of splicing occurs at this stage.

Translation

During translation, mRNA previously transcribed from DNA is decoded by specialized cellular structures called ribosomes to make proteins. Protein biosynthesis is divided into initiation, elongation and termination phases.

The ribosome has sites, which allow another specialized RNA molecule, known as tRNA, to bind to the mRNA. Binding of the correct tRNA to the mRNA on the ribosome is accomplished by an "anticodon" that is part of the tRNA. Thus, the correct tRNA, chemically linked to a specific amino acid, is directed to the ribosome to be added to a growing (nascent) polypeptide. The chemical process of connecting two amino acids is shown in the picture below.


The chemical process of connecting two amino acids resulting in a dipeptide and a water molecule

As the ribosome travels down the mRNA one codon at a time, another tRNA is attached to the mRNA at one of the ribosome sites. The first tRNA is released, but the amino acid that is attached to the first tRNA is now moved to the second tRNA, and binds to its amino acid. This translocation continues on, and a long chain of amino acid (protein), is formed.

When the entire unit reaches the stop codon on the mRNA, it falls apart and a newly formed protein is released. This is termination. It is important to know that during this process, many enzymes are used to either assist or facilitate the whole procedure.

Events following biosynthesis (Protein Synthesis)

The events following biosynthesis include post-translational modification and protein folding. During and after synthesis, polypeptide chains often fold to assume, so called, native secondary and tertiary structures. This is known as protein folding.

Many proteins undergo post-translational modification. This may include the formation of disulfide bridges or attachment of any of a number of biochemical functional groups, such as acetate, phosphate, various lipids and carbohydrates. Enzymes may also remove one or more amino acids from the leading (amino) end of the polypeptide chain, leaving a protein consisting of two polypeptide chains connected by disulfide bonds.

See also

- Genetic code

Genetic code

The *genetic code* is the set of rules by which information encoded in genetic material (DNA or RNA sequences) is translated into proteins (amino acid sequences) by living cells. Specifically, the code defines a mapping between tri-nucleotide sequences called *codons* and amino acids; every triplet of nucleotides in a nucleic acid sequence specifies a single amino acid. Most organisms use a nearly universal code that is referred to as the *standard genetic code*. Even viruses, which are not cellular and do not synthesize proteins themselves, have proteins made using this standard code. For a time, therefore, the code was thought to be universal. However, there are notable exceptions. It is also possible for a single organism to translate different parts of the genome in different ways. For example, in humans, protein synthesis in mitochondria relies on a modified genetic code that varies from the standard one.

Cracking the genetic code

After the structure of DNA was deciphered by James Watson, Francis Crick and Rosalind Franklin, serious efforts to understand the nature of the encoding of proteins began. George Gamov postulated that a three-letter code must be employed to encode the 20 different amino acids used by living cells to encode proteins. The first elucidation of a codon was done by Marshall Nirenberg and Heinrich J. Matthaei in 1961 at the National Institutes of Health. They used a cell-free system to translate a poly-uracil RNA sequence (or UUUUU... in biochemical terms) and discovered that the polypeptide they had synthesized consisted of only the amino acid phenylalanine. They, thereby deduced from this poly-phenylalanine that the codon UUU specified the amino-acid phenylalanine. Extending this work, Nirenberg and his coworkers were able to determine the nucleotide makeup of each codon. In order to determine the order of the sequence, trinucleotides were bound to ribosomes and radioactivaly labeled aminoacyl-tRNA was used to determine, which amino acid corresponded to the codon. Nirenberg's group was able to determine the the sequences of 54 out of 64 codons. Subsequent work by Har Gobind Khorana identified the rest of the code, and shortly thereafter Robert W. Holley determined the structure transfer RNA, the adapter molecule that facilitates translation. In 1968, Khorana, Holley and Nirenberg shared the Nobel Prize in Physiology or Medicine for their work.

Transfer of information via the genetic code

The genetic information carried by an organism, its genome, is inscribed in one or more DNA, or in some cases RNA, molecules. Each functional portion of a DNA or RNA molecule is referred to as a gene. The gene sequence inscribed in DNA, and in RNA, is composed of tri-

nucleotide units called codons, each coding for a single amino acid. Each nucleotide sub-unit consists of a phosphate, deoxyribose sugar and one of the 4 nitrogenous nucleotide bases grouped into 2 categories, purine and pyrimidine. The purine bases adenine (A) and guanine (G) are larger and consist of two aromatic rings. The pyrimidine bases cytosine (C) and thymine (T) are smaller and consist of only one aromatic ring. In RNA, however, thymine (T) is substituted by uracil (U), and the deoxyribose is substituted by ribose.

Each protein-coding gene is transcribed into a short template molecule of the related polymer RNA, known as messenger RNA or mRNA. This in turn is translated on the ribosome into an amino acid chain or polypeptide, which will then fold, resulting in secondary and tertiary structures. The process of translation requires transfer RNAs specific for individual amino acids with the amino acids covalently attached to them, guanosine triphosphate as an energy source, and a number of translation factors. tRNAs have anticodons complementary to the codons in mRNA and can be "charged" covalently with amino acids at their 3' terminal CCA ends. Individual tRNAs are charged with specific amino acids by enzymes known as aminoacyl tRNA synthetases which have high specificity for both their cognate amino acids and tRNAs. The high specificity of these enzymes is a major reasons why the fidelity of protein translation is maintained.

Theoretically, there are $4^3 = 64$ different codon combinations possible with a triplet codon of three nucleotides. In reality, all 64 codons of the standard genetic code are assigned for either amino acids or stop signals during translation. If, for example, an RNA sequence, UUUAAACCC is considered and the *reading-frame* starts with the first U (by convention, 5' to 3'), there are three codons, namely, UUU, AAA and CCC, each of which specifies one amino acid. This RNA sequence will be translated into an amino acid sequence, three amino acids long.

The standard genetic code is shown in the following tables. Table 1 shows what amino acid each of the 64 codons specifies. Table 2 shows what codons specify each of the 20 standard amino acids involved in translation. These are called forward and reverse codon tables, respectively. For example, the codon AAU represents the amino acid asparagine, and UGU and UGC represent cysteine {standard three-letter designations, Asn and Cys respectively).

Table 1: RNA codon table

This table shows the 64 codons and the amino acid each codon codes for. The direction is 5' to 3'.

		2nd base			
		U	C	A	G
1st base	U	UUU (Phe/F)Phenylalanine UUC (Phe/F)Phenylalanine UUA (Leu/L)Leucine UUG (Leu/L)Leucine	UCU (Ser/S)Serine UCC (Ser/S)Serine UCA (Ser/S)Serine UCG (Ser/S)Serine	UAU (Tyr/Y)Tyrosine UAC (Tyr/Y)Tyrosine UAA Ochre (*Stop*) UAG Amber (*Stop*)	UGU (Cys/C)Cysteine UGC (Cys/C)Cysteine UGA Opal (*Stop*) UGG (Trp/W)Tryptophan
	C	CUU (Leu/L)Leucine CUC (Leu/L)Leucine CUA (Leu/L)Leucine CUG (Leu/L)Leucine	CCU (Pro/P)Proline CCC (Pro/P)Proline CCA (Pro/P)Proline CCG (Pro/P)Proline	CAU (His/H)Histidine CAC (His/H)Histidine CAA (Gln/Q)Glutamine CAG (Gln/Q)Glutamine	CGU (Arg/R)Arginine CGC (Arg/R)Arginine CGA (Arg/R)Arginine CGG (Arg/R)Arginine
	A	AUU (Ile/I)Isoleucine AUC (Ile/I)Isoleucine AUA (Ile/I)Isoleucine AUG (Met/M)Methionine, *Start*[1]	ACU (Thr/T)Threonine ACC (Thr/T)Threonine ACA (Thr/T)Threonine ACG (Thr/T)Threonine	AAU (Asn/N)Asparagine AAC (Asn/N)Asparagine AAA (Lys/K)Lysine AAG (Lys/K)Lysine	AGU (Ser/S)Serine AGC (Ser/S)Serine AGA (Arg/R)Arginine AGG (Arg/R)Arginine
	G	GUU (Val/V)Valine GUC (Val/V)Valine GUA (Val/V)Valine GUG (Val/V)Valine	GCU (Ala/A)Alanine GCC (Ala/A)Alanine GCA (Ala/A)Alanine GCG (Ala/A)Alanine	GAU (Asp/D)Aspartic acid GAC (Asp/D)Aspartic acid GAA (Glu/E)Glutamic acid GAG (Glu/E)Glutamic acid	GGU (Gly/G)Glycine GGC (Gly/G)Glycine GGA (Gly/G)Glycine GGG (Gly/G)Glycine

Table 2: Reverse codon table

This table shows the 20 standard amino acids used in proteins, and the codons that code for each amino acid.

Ala	A	GCU, GCC, GCA, GCG	**Leu**	L	UUA, UUG, CUU, CUC, CUA, CUG
Arg	R	CGU, CGC, CGA, CGG, AGA, AGG	**Lys**	K	AAA, AAG
Asn	N	AAU, AAC	**Met**	M	AUG
Asp	D	GAU, GAC	**Phe**	F	UUU, UUC
Cys	C	UGU, UGC	**Pro**	P	CCU, CCC, CCA, CCG
Gln	Q	CAA, CAG	**Ser**	S	UCU, UCC, UCA, UCG, AGU,AGC
Glu	E	GAA, GAG	**Thr**	T	ACU, ACC, ACA, ACG
Gly	G	GGU, GGC, GGA, GGG	**Trp**	W	UGG
His	H	CAU, CAC	**Tyr**	Y	UAU, UAC
Ile	I	AUU, AUC, AUA	**Val**	V	GUU, GUC, GUA, GUG
Start		AUG	***Stop***		UAG, UGA, UAA

Salient features

Reading frame of a sequence

Note that a codon is defined by the inital nucleotide from which translation starts. For example, the string GGGAAACCC, if read from the first position, contains the codons GGG, AAA and CCC;and if read from the second position, it contains the codons GGA and AAC; if read starting from the third position, GAA and ACC. Partial codons have been ignored in this example. Every sequence can thus be read in three *reading frames*, each of which will produce a different amino acid sequence (in the given example, Gly-Lys-Pro, Gly-Asp, or Glu-Thr, respectively). With double-stranded DNA there are six possible reading frames, three in the forward orientation on one strand and three reverse, or on the opposite strand.

The actual frame a protein sequence is translated in is defined by a *start codon*, usually the first AUG codon in the mRNA sequence. Mutations that disrupt the reading frame by insertions or deletions of one or two nucleotide bases are known as frameshift mutations. These mutations may impair the function of the resulting protein, if it is formed, and are thus rare in in vivo protein-coding sequences. Often such misformed proteins are targeted for proteolytic degradation. One reason for the rareness of frame-shifted mutations being inherited is that if the protein being translated is essential for growth under the selective pressures the organism faces, absence of a functional protein may cause lethality before the organism is viable.

Start/stop codons

Translation starts with a chain initiation codon (start codon). Unlike stop codons, the codon alone is not sufficient to begin the process. Nearby sequences and initiation factors are also required to start translation. The most common start codon is AUG, which also codes for methionine, but other start codons are also used.

The three stop codons have been given names: UAG is amber, UGA is opal (sometimes also called umber), and UAA is ochre. "Amber" was named after its discoverer Harris Bernstein, whose last name means "amber" in German. The other two stop codons were named 'ochre" and "opal" in order to keep the "color names" theme. Stop codons are also called termination codons and they signal release of the nascent polypeptide from the ribosome due to binding of release factors in the absence of cognate tRNAs with anticodons complementary to these stop signals.[2]

Degeneracy of the genetic code

Many codons are *redundant*, meaning that two or more codons can code for the same amino acid. Degenerate codons may differ in their third positions; e.g., both GAA and GAG code for the amino acid glutamic acid. A codon is said to be *four-fold degenerate* if any nucleotide at its third position specifies the same amino acid; it is said to be *two-fold degenerate* if only two of four possible nucleotides at its third position specify the same amino acid. In two-fold degenerate codons, the equivalent third position nucleotides are always either two purines (A/G) or two pyrimidines (C/T). Only two amino acids are specified by a single codon; one of these is the amino-acid methionine, specified by the codon AUG, which also specifies the start of translation; the other is tryptophan, specified by the

codon UGG. The degeneracy of the genetic code is what accounts for the existence of silent mutations.

Degeneracy results because a triplet code designates 20 amino acids and a stop codon. Because there are four bases, triplet codons are required to produce at least 21 different codes. For example, if there were two bases per codon, then only 16 amino acids could be coded for (4^2=16). Because at least 21 codes are required, then 4^3 gives 64 possible codons, meaning that some degeneracy must exist.

These properties of the genetic code make it more fault-tolerant for point mutations. For example, in theory, four-fold degenerate codons can tolerate any point mutation at the third position, although codon usage bias restricts this in practice in many organisms; two-fold degenerate codons can tolerate one out of the three possible point mutations at the third position. Since transition mutations (purine to purine or pyrimidine to pyrimidine mutations) are more likely than transversion (purine to pyrimidine or vice-versa) mutations, the equivalence of purines or that of pyrimidines at two-fold degenerate sites adds a further fault-tolerance.

A practical consequence of redundancy is that some errors in the genetic code only cause a silent mutation or an error that would not affect the protein because the hydrophilicity or hydrophobicity is maintained by equivalent substitution of amino acids; for example, a codon of NUN (where N = any nucleotide) tends to code for hydrophobic amino acids. Even so, it is a single point mutation that causes a modified hemoglobin molecule in sickle-cell disease. The hydrophilic glutamate (Glu) is substituted by the hydrophobic valine (Val), which reduces the solubility of ß-globin. In this case, this mutation causes hemoglobin to form linear polymers linked by the hydrophobic interaction between the valine groups causing sickle-cell deformation of erythrocytes. Sickle-cell disease is generally not caused by a de novo mutation. Rather it is selected for in malarial regions (in a similar way to thalassemia), as heterozygous people have some resistance to the malarial Plasmodium parasite (heterozygote advantage).

These variable codes for amino acids are allowed because of modified bases in the first base of the anticodon of the tRNA, and the base-pair formed is called a wobble base pair. The modified bases include inosine and the Non-Watson-Crick U-G basepair.

Variations

Numerous variations of the standard genetic code are found in mitochondria, which are energy-producing organelles that are found inside eukaryotic cells. Mycoplasma translate the codon UGA as tryptophan. Ciliate protozoa also have some variation in the genetic code: UAG and often UAA code for glutamine (a variant also found in some green algae), or UGA codes for cysteine. Another variant is found in some species of the yeast, Candida, where CUG codes for serine. In addition in some rare cases certain proteins may also use alternate initiation (start) codons.

In certain proteins, non-standard amino acids are substituted for standard stop codons, depending upon associated signal sequences in the messenger RNA: UGA can code for selenocysteine and UAG can code for pyrrolysine as discussed in the relevant articles. A detailed description of variations in the genetic code can be found at the NCBI web site. However, there may be other non-standard interpretations that are not yet known.

Sequencing of genomes may reveal unique genetic codes that allow the incorporation of other novel amino acids into proteins.

Origin of the genetic code

Despite the variations that exist, the genetic codes used by all known forms of life on Earth are very similar. Since there are many possible genetic codes that are thought to have similar utility to the one used by Earth life, the theory of evolution suggests that the genetic code was established very early in the history of life.

One can ask the question: is the genetic code completely random, just one set of codon-amino acid correspondences that happened to establish itself and be "frozen in" early in evolution, although functionally any of the many other possible transcription tables would have done just as well? Already a cursory look at the table shows patterns that suggest that this is not the case.

There are three themes running through the many theories that seek to explain the evolution of the genetic code (and hence the origin of these patterns).[3] One is illustrated by recent aptamer experiments which show that some amino acids have a selective chemical affinity for the base triplets that code for them.[4] This suggests that the current, complex transcription mechanism involving tRNA and associated enzymes may be a later development, and that originally, protein sequences were directly templated on base sequences. Another is that the standard genetic code that we see today grew from a simpler, earlier code through a process of "biosynthetic expansion". Here the idea is that primordial life 'invented' new amino acids (e.g. as by-products of metabolism) and later back-incorporated some of these into the machinery of genetic coding. Although much circumstantial evidence has been found to indicate that originally the number of different amino acids used may have been considerably smaller than today,[5] precise and detailed hypotheses about exactly which amino acids entered the code in exactly what order has proved far more controversial.[6][7] A third is that natural selection organized the codon assignments of the genetic code to minimize the effects of genetic errors (mutations).[8]

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See also

- Protein biosynthesis

Transcription factor

In molecular biology, a *transcription factor* is a protein that acts as a regulator of gene expression, specifically regulating the activation or inhibition of transcription in the eukaryotic nucleus. Transcription factors localise to regions of promoter and enhancer sequence elements either through direct binding to DNA or through binding other DNA-bound proteins. They act by promoting or inhibiting the formation of the preinitiation complex (PIC) that recruits and activates RNA polymerase.

The regulation of transcription factors is a highly complex process as it is dependent upon a number of events, most notable of which are the presence of other DNA binding proteins (including other transcription factors) as well as local chromatin structure. Initial models, based on in vitro exprriments suggested that there is a definite assembly sequence of transcription factors dictated by the DNA sequence. It is, however, becoming incresingly obvious that the events leading to activation of transcription are dependent on a large number of factors and are highly intertwined. Furthermore epigenetic information present on DNA appears to play an important role in transcriptional activation.

Classes

There are three classes of transcription factors:

- General transcription factors are involved in the formation of a preinitiation complex. The most common are abbreviated as TFIIA, TFIIB, TFIID, TFIIE, TFIIF, TFIIH. They are ubiquitous and interact with the core promoter region surrounding the transcription start site(s) of all class II genes.

- *Upstream transcription factors* are proteins that bind somewhere upstream of the initiation site to stimulate or repress transcription.
- *Inducible transcription factors* are similar to upstream transcription factors but require activation or inhibition.

General Definition- Protein involved in recognition by RNA polymerases of specific regulatory sequences in eukaryotic genes.

DNA motifs found in transcription factors

- Helix-turn-helix (HTH) bind the major groove of the DNA. Zinc fingers function as structural platforms for DNA binding. Leucine zippers function in associating the transcription factors with each other. Basic-helix-loop-helix (bHLH) bind DNA with two alpha helices containing basic amino acid residues which are linked by a loop and are typically dimeric. G-quadruplex Motifs are a focus for current studies in their role as a TF binding site.

Examples of transcription factors

STAT

The Signal Transducers and Activator of Transcription (STAT) proteins regulate many aspects of cell growth, survival and differentiation. The transcription factors of this family are activated by the Janus Kinase JAK and dysregulation of this pathway is frequently observed in primary tumors and leads to increased angiogenesis and enhanced survival of tumors. Knockout studies have provided evidence that STAT proteins are involved in the development and function of the immune system and play a role in maintaining immune tolerance and tumor surveillance.

Function of STAT proteins

STAT proteins were originally described as latent cytoplasmic transcription factors that require phosphorylation for nuclear retention. The unphosphorylated STAT proteins shuttle between the cytosol and the nucleus waiting for its activation signal. Once the activated transcription factors reach the nucleus, they bind to a consensus DNA-recognition motif called gamma activated sites (GAS) in the promoter region of cytokine-inducible genes and activate transcription of these genes.

Activation of STAT proteins

Extracellular binding of Cytokines induces activation of the intracellular Janus kinase that phosphorylates a specific tyrosine residue in the STAT protein which promotes the dimerization of STAT monomers via their SH2 domain. The phosphorylated dimer is then

actively transported in the nucleus via importin a/b and RanGDP complex. Once inside the nucleus the active STAT dimer binds to cytokine inducible promoter regions of genes containing gamma activated site (GAS) motif and activate transcription of this proteins. The STAT protein can be dephosphorylated by nuclear phosphatases which leads to inactivation of STAT and the transcription factor becomes transported out of the nucleus by exportin crm1/RanGTP.

Stem cells

Stem cells are primal cells that retain the ability to renew themselves through cell division and can differentiate into a wide range of specialized cell types. Research in the stem cell field grew out of findings by Canadian scientists Ernest A. McCulloch and James E. Till in the 1960s.

The two categories of stem cells include embryonic stem cells and adult stem cells and possibly a third, cord-blood-derived embryonic-like stem cells (CBEs). In a blastocyst of a developing embryo, stem cells differentiate into all of the specialised embryonic tissues. In adult organisms, stem cells and progenitor cells act as a repair system for the body, replenishing specialized cells. As stem cells can be readily grown and transformed into specialized tissues such as muscles or nerves through cell culture, their use in medical therapies has been proposed.

Stem cell properties

Defining properties

The rigorous definition of a *stem cell* requires that it possesses two properties:

- *Self-renewal* - the ability to go through numerous cycles of cell division while maintaining the undifferentiated state.
- *Unlimited potency* - the capacity to differentiate into any mature cell type. In a strict sense, this makes stem cells either *totipotent* or *pluripotent*, although some *multipotent* and/or *unipotent* progenitor cells are sometimes referred to as stem cells.

These properties can be illustrated in vitro, using methods such as clonogenic assays, where the progeny of single cell is characterized. However, in vitro culture conditions can alter the behavior of cells, making it unclear whether the cells will behave in a similar manner in vivo. Considerable debate exists whether some proposed adult cell populations are truly stem cells.

Potency definitions

Potency specifies the differentiation potential (the potential to differentiate into different cell types) of the stem cell.

- *Totipotent* stem cells are produced from the fusion of an egg and sperm cell. Cells produced by the first few divisions of the fertilized egg cell are also totipotent. These cells can differentiate into embryonic and extraembryonic cell types.
- *Pluripotent* stem cells are the descendants of totipotent cells and can differentiate into cells derived from the three germ layers.
- *Multipotent* stem cells can produce only cells of a closely related family of cells (e.g. hematopoietic stem cells differentiate into red blood cells, white blood cells, platelets, etc.).
- *Unipotent* cells can produce only one cell type, but have the property of self-renewal which distinguishes them from non-stem cells.

Embryonic stem cells

Embryonic stem cells (ES cells) are stem cells derived from the inner cell mass of a blastocyst. A blastocyst is an early stage embryo - approximately 4 to 5 days old in humans and consisting of 50-150 cells. ES cells are pluripotent, and give rise during development all derivatives of the three primary germ layers: ectoderm, endoderm and mesoderm. In other words, they can develop into each of the more than 200 cell types of the adult body when given sufficient and necessary stimulation for a specific cell type. They do not contribute to the extra-embryonic membranes or the placenta.

When given no stimuli for differentiation, ES cells will continue to divide in vitro and each daughter cell will remain pluripotent. The pluripotency of ES cells has been rigorously demonstrated in vitro and in vivo, thus they can be indeed classified as stem cells.

Because of their unique combined abilities of unlimited expansion and pluripotency, embryonic stem cells are a potential source for regenerative medicine and tissue replacement after injury or disease. To date, no approved medical treatments have been derived from embryonic stem cell research. This is not surprising considering that many nations currently have a moratorium on either ES cell research or the production of new ES cell lines.

Adult stem cells

Adult stem cells are undifferentiated cells found throughout the body that divide to replenish dying cells and regenerate damaged tissues. Also known as *somatic* (from Greek £É¼±Ä¹ºóÂ, of the body) stem cells, they can be found in children, as well as adults.

A great deal of adult stem cell research has focused on clarifying their capacity to divide or self-renew indefinitely and their differentiation potential. Many adult stem cells may be better classified as progenitor cells, due to their limited capacity for cellular differentiation.

Nevertheless, specific multipotent or even unipotent adult progenitors may have potential utility in regenerative medicine. The use of adult stem cells in research and therapy is not as controversial as embryonic stem cells, because the production of adult stem cells does not require the destruction of an embryo. In contrast with the embryonic stem cell research, more US government funding has been provided for adult stem cell research. Adult

stem cells can be isolated from a tissue sample obtained from an adult. They have mainly been studied in humans and model organisms such as mice and rats.

Lineage

To ensure self-renewal, stem cells undergo two types of cell division (see Stem cell division and differentiation diagram). Symmetric division gives rise to two identical daughter cells both endowed with stem cell properties. Asymmetric division, on the other hand, produces only one stem cell and a progenitor cell with limited self-renewal potential. Progentiors can go through several rounds of cell division before terminally differentiating into a mature cell. It is believed that the molecular distinction between symmetric and asymmetric divisions lies in differential segregation of cell membrane proteins (such as receptors) between the daughter cells.

Treatments

Medical researchers believe that stem cell research has the potential to change the face of human disease. A number of current treatments already exist, although the majority of them are not commonly used because they tend to be experimental and not very cost-effective. Medical researchers anticipate being able to use technologies derived from stem cell research to treat cancer, parkinson's disease, spinal cord injuries, and muscle damage, amongst a number of other diseases, impairments and conditions. However, there still exists a great deal of social and scientific uncertainty surrounding stem cell research, which could possibly be overcome through public debate and future research.

Stem cells, however, are already used extensively in research, and some scientists do not see cell therapy as the first goal of the research, but see the investigation of stem cells as a goal worthy in itself.

Controversy surrounding stem cell research

There exists a widespread controversy over stem cell research that emanates from the techniques used in the creation and usage of stem cells. Embryonic stem cell research is particularly controversial because, with the present state of technology, starting a stem cell line requires the destruction of a human embryo and/or therapeutic cloning. Opponents of the research argue that this practice is a slippery slope to reproductive cloning and tantamount to the instrumentalization of a human being. Contrarily, medical researchers in the field argue that it is necessary to pursue embryonic stem cell research because the resultant technologies are expected to have significant medical potential, and that the embryos used for research are only those slated for destruction anyway. The ensuing debate has prompted authorities around the world to seek regulatory frameworks and highlighted the fact that stem cell research represents a social and ethical challenge.

Key events in stem cell research

- 1960s - Joseph Altman and Gopal Das present evidence of adult neurogenesis, ongoing stem cell activity in the brain; their reports contradict Cajal's "no new neurons" dogma are largely ignored
1963 - McCulloch and Till illustrate the presence of self-renewing stem cells in mouse bone marrow
1968 - bone marrow transplant between two siblings successfully treats SCID
1978 - haematopoietic stem cells are discovered in human cord blood
1981 - mouse embryonic stem cells are derived from the inner cell mass
1992 - neural stem cells are cultured in vitro as neurospheres
1995 - President Bill Clinton signs into law the Dickey Amendment which makes it illegal for Federal money to be used for research where stem cells are derived from the destruction of the embryo.
1997 - leukemia is shown to originate from a haematopoietic stem cell, the first direct evidence for cancer stem cells
1998 - James Thomson and coworkers derive the first human embryonic stem cell line at the University of Wisconsin-Madison.
2000s - several reports of adult stem cell plasticity are published
2003 - Dr. Songtao Shi of NIH discovers new source of adult stem cells in children's primary teeth[1]
2004-2005 - Hwang Woo-Suk claims to have created several human embryonic stem cell lines from unfertilised human oocytes. The lines are later shown to be fabricated
2005 - Researchers at Kingston University in England claim to have discovered a third category of stem cell, dubbed cord-blood-derived embryoniclike stem cells (CBEs), derived from umbilical cord blood. The group claims these cells are able to differentiate into more types of tissue than adult stem cells.
2001-2006 - President George W. Bush is the first president to provide federal funding for embryonic stem cell research totaling approximately $100 Million.
July 19, 2006 - President George W. Bush vetoes H.R. 810, a bill that would have reversed the Clinton-era law which made it illegal for Federal money to be used for research where stem cells are derived from the destruction of an embryo.

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Vaccination

Vaccination is the process of administering weakened or dead pathogens to a healthy person or animal, with the intent of conferring immunity against a targeted form of a related disease agent. It succeeded and is distinct from inoculation.

The term was coined by Edward Jenner and adapted by Louis Pasteur for his pioneering work in vaccination. Vaccination (Latin: vacca—cow) is so named because the first vaccine was derived from a virus affecting cows: the cowpox virus, a relatively benign virus that provides a degree of immunity to smallpox, a contagious and deadly disease. In common speech, 'vaccination' and 'immunization' generally have the same colloquial meaning.

Vaccination efforts have been met with some resistance since its inception. Early success and compulsion brought widespread acceptance and mass vaccination campaigns were undertaken which have greatly reduced the incidence of many diseases in many areas. The eradication of smallpox, which was last seen in a natural case in 1977, is considered the most spectacular success of vaccination. Currently some people assert that childhood vaccination causes some autoimmune disease and autism. Scientific studies have not demonstrated a link, however, the assertion found space in a United States House of Representatives report in 2003 which included the suggestion that mercury derivatives in vaccines might have been a cause of autism.

Triggering immune sensitization

In the generic sense, the process of artificial induction of immunity, in an effort to protect against infectious disease, works by 'priming' the immune system with an 'immunogen'. Stimulating immune response, via use of an infectious agent, is known as immunization. Vaccinations involve the administration of one or more immunogens, in the form of live, but weakened (attenuated) infectious agents, which normally are either weaker, but closely-related species (as with smallpox and cowpox), or strains weakened by some process. In such cases, an immunogen is called a vaccine.

Some modern vaccines are administered after the patient already has contracted a disease, as in the cases of experimental AIDS, cancer and Alzheimer's disease vaccines. Vaccinia given after exposure to smallpox, within the first four days, is reported to attenuate the disease considerably, and vaccination within the first week is known to be beneficial to a degree. The first Rabies immunisation was given by Pasteur to a child bitten by a rabid dog, and then and subsequently post-exposure immunisation to Rabies has generally been followed by survival. The essential empiricism behind such immunizations is that the vaccine triggers an immune response more rapidly than the natural infection itself.

Most vaccines are given by hypodermic injection as they are not absorbed reliably through the gut. Live attenuated Polio, some Typhoid and Cholera Vaccines are given orally in order to produce immunity based in the bowel.

History of vaccinations

Vaccination campaigns have spread throughout the globe since Jenner's smallpox vaccine of 1796, sometimes prescribed by law or regulations. Vaccines are now used to fight a wide variety of disease threats besides smallpox. Louis Pasteur further developed the technique during the 19th century, extending its use to protecting against bacterial anthrax and viral rabies. The method Pasteur used entailed treating the infectious agents for those diseases so they lost the ability to cause serious disease. Pasteur adopted the name vaccine as a generic term in honor of Jenner's discovery, which Pasteur's work built upon.

Prior to vaccination with cowpox, the only known protection against smallpox was inoculation or variolation (Variola - the Smallpox viruses) where a small amount of live smallpox virus was administered to the patient; this carried the serious risk that the patient would be killed or seriously ill. The death rate from variolation was reported to be around a tenth of that from natural infection with Variola, and the immunity provided was considered quite reliable. Factors contributing to the efficacy of variolation probably include the choices of Variola Minor strains used, the relatively low number of cells infected in the first phase of multiplication following initial exposure, and the exposure route used, via the skin or nasal lining rather than inhalation of droplets into the lungs.

Consistency would suggest the activity should have predated Jenner's description of an effective vaccination system, and there is some history relating to opposition to the older and more hazardous procedure of variolation.

In modern times, the first vaccine-preventible disease targeted for eradication was smallpox. The World Health Organization coordinated the global effort to eradicate this disease. The last naturally occurring case of smallpox occurred in Somalia in 1977.

In 1988, the governing body of W.H.O. targeted polio for eradication by the year 2000. Although the target was missed, eradication is very close. The next eradication target would most likely be measles, which has declined since the introduction of measles vaccination in 1963.

In 2000, the Global Alliance for Vaccines and Immunization was established to strengthen routine vaccinations and introduce new and under-used vaccines in countries with a per capita GDP of under US$1000. GAVI is now entering its second phase of funding, which extends through 2014.

Compulsory vaccination and opposition to vaccination

In an attempt to eliminate the risk of outbreaks of some diseases, several governments and other institutions have instituted policies requiring vaccination for all people. For example, an 1853 law required universal vaccination against smallpox in England and Wales, with fines levied on people who did not comply. In the United States, the Supreme Court ruled in the 1905 case Jacobson v. Commonwealth of Massachusetts that the state could require individuals to be vaccinated for the common good. Common contemporary vaccination policies require that children receive common vaccinations before entering school. Compulsory vaccination is believed to have greatly reduced the rates of some infectious diseases.[1]

Beginning with early vaccination in the nineteenth century, these policies led to resistance from a variety of groups, collectively called anti-vaccinationists, who objected on ethical, political, medical safety, religious, and other grounds. Common objections are that compulsory vaccination represents excessive government intervention in personal matters, or that the proposed vaccinations are not sufficiently safe. Many modern vaccination policies allow exemptions for people who have compromised immune systems, allergies to the components used in vaccinations or strongly-held objections.[1]

In 1904 in the city of Rio de Janeiro, Brazil a government program of mandatory smallpox vaccination resulted in the so-called Vaccine Revolt, several days of rioting with considerable property damage and a number of deaths.

Herd immunity and medical risk management issues

Vaccination campaigns are generally accepted as having contributed to the worldwide elimination of smallpox, through herd immunity, and to the restriction of polio to isolated pockets in countries where healthcare access is difficult. The risk management practices of government health agencies' promoting widespread vaccination campaigns has prompted increasing controversy in recent years, despite the fact that many once-common childhood diseases, such as mumps, measles and rubella, are now relatively rare in developed countries.

Nevertheless, vaccination campaigns may have unfortunate co-evolutionary side-effects, particularly if they produce a selective pressure in favor of certain strains against which there are no vaccines or treatment. Another problem related to co-evolution is that vaccines that may eliminate one infectious diseases or another may, in turn, allow others to thrive in the ecological niche that has been vacated. For example, it has been postulated that (the less-often-fatal) serogroup-B meningitis strains may expand into the niche provided if serogroup-C is largely eradicated through vaccination. However, while there has been a rise in serogroup-B meningitis, there is as yet no evidence to link this to the meningitis-C vaccination.

An incompletely-successful attempt at eradication of a disease through vaccination might increase the average age of contraction of the disease. In diseases such as measles, where there is a higher rate of complication in older people, the overall effect might, in theory, be to cause more deaths than before the vaccination was introduced. Potentially, this could be a 'perverse effect' of vaccination campaigns. Observation of immunity levels in a population over many years has been followed by booster immunization programs, for instance, in the United Kingdom, with measles and mumps.

Adjuvants and preservatives

Vaccines typically contain one or more adjuvants, used to boost the immune response. Tetanus toxoid for instance is usually adsorbed onto Alum. This presents the antigen in such a way as to produce a greater action than the simple aqueous tetanus toxoid. People who get an excessive reaction to adsorbed tetanus toxoid may be given the simple vaccine when time for a booster occurs.

In the preparation for the 1990 Gulf campaign, Pertussis vaccine (not acellular) was used as an adjuvant for Anthrax vaccine. This produces a more rapid immune response than giving only the Anthrax, which is of some benefit if exposure might be imminent.

They may also contain preservatives, which are used to prevent contamination with bacteria or fungi. Until recent years, the preservative thiomersal was used in many vaccines that did not contain live virus. As of 2005, the only childhood vaccine in the U.S.A. that contains thiomerosal is the influenza vaccine [2], which is currently recommended only for children with certain risk factors.[2] The UK is considering Influenza immunisation in children perhaps as soon as in 2006-7. Single-dose Influenza vaccines supplied in the UK do not list Thiomersal (its UK name) in the ingredients. Preservatives may be used at various stages of production of vaccines, and the most sophisticated methods of measurement might

detect traces of them in the finished product, as they may in the environment and population as a whole[3].

Vaccine research

Some major contemporary research in vaccination focuses on development of vaccinations for diseases including HIV and malaria.

Vaccine is an international peer-reviewed journal for vaccination researchers, indexed in Medline pISSN: 0264-410X.

See also

- Vaccine controversy

References

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Vaccines

A *vaccine* is an antigenic preparation used to establish immunity to a disease. The term derives from Edward Jenner's use of cowpox ("vacca" means cow in Latin), which, when administered to humans, provided them protection against smallpox, which Pasteur and others perpetuated. The process of distributing and administrating vaccines is referred to as vaccination.

Vaccines can be prophylactic (e.g. to prevent or ameliorate the effects of a future infection by any natural or "wild" pathogen), or therapeutic (e.g. vaccines against cancer are also being investigated).

Types of vaccines

Vaccines may be living, weakened strains of viruses or bacteria that intentionally give rise to unapparent-to-trivial infections. Vaccines may also be killed or inactivated organisms or purified products derived from them.

There are four types of traditional vaccines:

- Inactivated - these are previously virulent micro-organisms that have been killed with chemicals or heat. Examples are vaccines against flu, cholera, bubonic plague, and hepatitis A. Most such vaccines may have incomplete or short-lived immune responses and are likely to require booster shots.
- Live, attenuated - these are live micro-organisms that have been cultivated under conditions that disable their virulent properties. They typically provoke more durable immunological responses and are the preferred type for healthy adults. Examples include yellow fever, measles, rubella, and mumps.
- Toxoids - these are inactivated toxic compounds from micro-organisms in cases where these (rather than the micro-organism itself) cause illness. Examples of toxoid-based vaccines include tetanus and diphtheria.
- Subunit - rather than introducing a whole inactivated or attenuated micro-organism to an immune system, a fragment of it can create an immune

response. Characteristic example is the subunit vaccine against HBV that is composed of only the surface proteins of the virus (produced in yeast)

The live tuberculosis vaccine is not the contagious TB strain, but a related strain called "BCG"; it is used in the United States very infrequently.

A number of innovative vaccines are also in development and in use:

- Conjugate - certain bacteria have polysaccharide outer coats that are poorly immunogenic. By linking these outer coats to proteins (e.g. toxins), the immune system can be led to recognize the polysaccharide as if it were a protein antigen. This approach is used in the Haemophilus influenzae type B vaccine.
- Recombinant Vector - by combining the physiology of one micro-organism and the DNA of the other, immunity can be created against diseases that have complex infection processes
- DNA vaccination - in recent years a new type of vaccine, created from an infectious agent's DNA called DNA vaccination, has been developed. It works by insertion (and expression, triggering immune system recognition) into human or animal cells, of viral or bacterial DNA. Some cells of the immune system that recognize the proteins expressed will mount an attack against these proteins and cells expressing them. Because these cells live for a very long time, if the pathogen that normally expresses these proteins is encountered at a later time, they will be attacked instantly by the immune system. One advantage of DNA vaccines is that they are very easy to produce and store. As of 2006, DNA vaccination is still experimental, but shows some promising results.

Note that while most vaccines are created using inactivated or attenuated compounds from micro-organisms, synthetic vaccines are composed mainly or wholly of synthetic peptides, carbohydrates or antigens.

Developing immunity

The immune system recognizes vaccine agents as foreign, destroys them, and 'remembers' them. When the virulent version of an agent comes along, the immune system is thus prepared to respond, by (1) neutralizing the target agent before it can enter cells, and (2) by recognizing and destroying infected cells before that agent can multiply to vast numbers.

Vaccines have contributed to the eradication of smallpox, one of the most contagious and deadly diseases known to man. Other diseases such as rubella, polio, measles, mumps, chickenpox, and typhoid are nowhere near as common as they were just a hundred years ago. As long as the vast majority of people are vaccinated, it is much more difficult for an outbreak of disease to occur, let alone spread. This effect is called herd immunity. Polio, which is transmitted only between humans, is targeted by an extensive eradication campaign that has seen endemic polio restricted to only parts of four countries. The difficulty of reaching all children, however, has caused the eradication date to be missed twice by 2006.

Vaccination schedule

In order to provide best protection, children are recommended to receive vaccinations as soon as their immune systems are sufficiently developed to respond to particular vaccines, with additional 'booster' shots often required to achieve 'full immunity'. This has led to the development of complex vaccination schedules. In the United States, the Advisory Committee on Immunization Practices, which recommends schedule additions for the Center for Disease Control, recommends routine vaccination of children against: hepatitis A, hepatitis B, polio, mumps, measles, rubella, diphtheria, pertussis, tetanus, HiB, chicken pox, rotavirus, influenza, meningococcal disease and pneumonia. The large number of vaccines and boosters recommended (up to 24 injections by age two) has led to problems with achieving full compliance. In order to combat declining compliance rates, various notification systems have been instituted and a number of combination injections are now marketed (e.g., Prevnar and ProQuad vaccines), which provide protection against multiple diseases. Complete scheduled vaccinations may be a requirement for school admission at various grades. In the US, there are varying exemptions that may be claimed by parents, for religious or other reasons.

Besides recommendations for infant vaccination boosters, many specific vaccines are recommended for repeated injections throughout life -- most commonly for measles, tetanus, influenza, and pneumonia. Pregnant women are often screened for continued resistance to rubella. In 2006, a vaccine was introduced against shingles, a disease caused by the chicken pox virus, which usually affects the elderly. Vaccine recommendations for the elderly concentrate on pneumonia and influenza, which are more deadly to that group.

Vaccine Controversies

Main article: Vaccine controversy

Opposition to vaccination, from a wide array of vaccine critics, has existed since the earliest vaccination campaigns:

A number of vaccines, including those given to very young children, have contained thimerosal, a preservative that metabolizes into ethylmercury. It has been used in some influenza, DTP (diphtheria, tetanus and pertussis) vaccine formulations. Since 1997, use of thimerosal has been gradually diminishing in western industrialized countries after recommendations by medical authorities, but trace amounts of thimerosal remain in many vaccines and in some vaccines, thimerosal has not yet been phased out despite recommendations. Some states in USA have enacted laws banning the use of thimerosal in childhood vaccines.

In the late 1990s, controversy over vaccines escalated in both the US and the United Kingdom when a study, published in the respected journal Lancet, by Dr. Andrew Wakefield suggested a possible link between bowel disorders, autism and MMR vaccine, and urged further research. His report, which focused upon a novel syndrome he described as autistic enterocolitis, garnered significant media attention, leading to a drop in the uptake of the MMR vaccine in the UK and some other countries. The study garnered criticism for its small sample size, and for failing to use healthy controls. In response to the controversies, a

number of studies with larger sample sizes were conducted, and failed to confirm the findings. In 2004, 10 of the 13 authors of the original Wakefield study retracted the paper's interpretation, without disputing the central finding of a consistent set of bowel disorders among the autistic study subjects, stating the data were insufficient to establish a causal link between MMR vaccine and autism. Wakefield was also later found to have received a substantial sum from trial lawyers to fund this research further calling into question the validity of its findings. Also in 2004, the United States' Institute of Medicine reported that evidence "favors rejection" of any link between vaccines containing thimerosal, or MMR, and the development of autism.

In 2004 and 2005, England and Wales experienced an increase in the incidence of mumps infections among adolescents and young adults. The age group affected were too old to have received the routine MMR immunisations around the time Wakefield et al's paper was published, and too young to have contracted natural mumps as a child, and thus to achieve a herd immunity effect. With the decline in mumps that followed the introduction of the MMR vaccine, these individuals had not been exposed to the disease, but still had no immunity, either natural or vaccine induced. Therefore, when the disease re-emerged as immunization rates declined following the controversy, they were susceptible to infection. This and similar examples indicate the importance of:

1. careful modelling to anticipate the impact that an immunisation campaign will have on the epidemiology of the disease in the medium to long term
2. ongoing surveillance for the relevant disease following introduction of a new vaccine and
3. maintaining high immunisation rates, even when a disease has become rare.

There is opposition to vaccination (of any type) from some sectors of the community, particularly those who favour 'alternative' health care. Often this opposition is not based on specific data or details but rather a general leaning against conventional medicine and science. Naturopaths and other alternative health care practitioners sometimes offer their own, alternative treatments to conventional vaccination.

In Australia, a massive increase in vaccination rates was observed when the federal government made certain benefits (such as the universal 'Family Allowance' welfare payments for parents of children) dependent on vaccination. As well, children were not allowed into school unless they were either vaccinated or their parents completed a statutory declaration refusing to immunize them, after discussion with a doctor, and other bureaucracy. (Similar school-entry vaccination regulations have been in place in some parts of Canada for several years.) It became easier and cheaper to vaccinate one's children than not to. When faced with the annoyance, many more casual objectors simply gave in.

Potential for adverse side effects in general

Some refuse to immunize themselves or their children, because they believe certain vaccines' adverse side effects outweigh their benefits. A variation of this reasoning is that not enough is known of the adverse effects to determine whether the potential benefits make

the risks worthwhile. Since most people are vaccinated against contagious and potentially fatal diseases, the chances of someone who is not vaccinated becoming ill is a good deal smaller than it might be if their opinion was held by more people. Therefore, they acquire some of the benefits of vaccines through herd immunity without assuming the risks those who choose to vaccinate do.

Advocates of recommended routine vaccination argue that side effects of most approved vaccines are either far less serious than actually catching the disease, or are very rare, and argue that the calculus of risk/benefit ratio should be based on benefit to humanity rather than simply on the benefit to the immunized individual. The main risk of rubella, for example, is to the fetuses of pregnant women, but this risk can be effectively reduced by the immunization of children to prevent transmission to pregnant women.

Efficacy of vaccines

Vaccines do not guarantee complete protection from a disease. Even after a vaccination, there is still a possibility that a vaccinated person may get the disease. Sometimes this is because the host's immune system simply doesn't respond adequately or at all. This is known in medical jargon as a 'low titre of antibodies'. This may be due to a lowered immunity in general (diabetes, steroid use, HIV infection) or just bad luck (the host's immune system does not have a B-cell capable of generating antibodies to that antigen).

Even if the host develops antibodies, the human immune system is not perfect. Some germs can mutate (the common cold and influenza viruses are highly efficient at this), and in any case the immune system might still not be able to defeat the infection.

Adjuvants are typically used to boost immune response. The efficacy or performance of the vaccine is dependent on a number of factors:

- the disease itself (for some diseases vaccination performs better than for other diseases)
- the strain of vaccine (some vaccinations are for different strains of the disease)
- whether one kept to the timetable for the vaccinations
- some individuals are 'non-responders' to certain vaccines, meaning that they do not generate antibodies even after being vaccinated correctly
- other factors such as ethnicity or genetic predisposition

In cases where a vaccinated individual does develop the disease vaccinated against, the disease is likely to be milder than without vaccination.

Adverse effects (known and suspected)

Some autoimmune diseases like Acute disseminated encephalomyelitis, Guillain-Barré syndrome, Transverse myelitis and multiple sclerosis are known to be connected to vaccines, which suggests other autoimmune disorders might also be vaccine-related **[1]** **[2]**

Economics of vaccine development

One challenge in vaccine development is economic: many of the diseases most demanding a vaccine, including HIV, malaria and tuberculosis, exist principally in poor countries. Although some contend pharmaceutical firms and biotech companies have little incentive to develop vaccines for these diseases, because there is little revenue potential, the number of vaccines actually administered has risen dramatically in recent decades. This increase, particularly in the number of different vaccines administered to children before entry into schools may be due to government mandates, rather than economic incentive. Most vaccine development to date has relied on 'push' funding by government and non-profit organizations, of government agencies, universities and non-profit organizations.

Many researchers and policymakers are calling for a different approach, using 'pull' mechanisms to motivate industry. Mechanisms such as prizes, tax credits, or advance market commitments could ensure a financial return to firms that successfully developed an HIV vaccine. If the policy were well-designed, it might also ensure people have access to a vaccine if and when it is developed.

Preservatives

In order to extend shelf life and reduce production and storage costs, thimerosal, a mercury-containing organic compound, was used routinely until recent years as a preservative. Thimerosal was gradually being phased out in the U.S. (it has been phased out in other countries, e.g. Denmark in 1992), but may be used in stages of manufacture. Parents wishing to avoid this preservative, most common in multi-dose containers of influenza vaccine, may specifically ask for thimerosal-free alternatives that contain only trace amounts. The mercury-free vaccines are, however, extremely difficult for parents to find. Often health care workers have insufficient knowledge needed to discuss the issue with parents, and often they will report to parents that vaccines are mercury free when in fact that is not the case. Recently, the Bush Administration has taken measures to drastically ease many regulations preventing mercury from being put into vaccines, and also has taken measures to permit industrial producers to use levels of mercury in vaccines much higher than previously permitted. Mercury is the leading candidate for the widely discussed autism epidemic currently afflicting children, and, as has been noted by many researchers, children who are unvaccinated (such as some Amish groups), have drastically reduced autism rates as compared to children who are vaccinated.

List of Vaccines

GIDEON's vaccine list and vaccine trade name listc and Health Professionals: Information about vaccine preventable diseases', Immunization Action Coalition

Chickenpox

Classifications and external resources

ICD-10

B01.

ICD-9

052

DiseasesDB

29118

MedlinePlus

001592

eMedicine

ped/2385 derm/74**,** emerg/367

MeSH

C02.256.466.175

Chickenpox, also spelled *chicken pox*, is the common name for Varicella simplex, classically one of the childhood infectious diseases caught and survived by most children.

Chickenpox is caused by the varicella-zoster virus (VZV), also known as human herpes virus 3 (HHV-3), one of the eight herpes viruses known to affect humans. It starts with conjunctival and catarrhal symptoms, moderate fever and then characteristic spots appearing in two or three waves, mainly on the body and head rather than the hands and becoming itchy raw pox (pocks), small open sores which heal mostly without scarring.

Chickenpox has a two-week incubation period and is highly contagious by air transmission two days before symptoms appear. Following primary infection there is usually lifelong protective immunity from further episodes of chickenpox. Recurrent chickenpox is fairly rare but more likely in people with compromised immune systems.

Symptomatic treatment, with calamine lotion to ease itching and paracetamol (known in the U.S. as acetaminophen) to reduce fever, is widely used.

Chickenpox is rarely fatal (usually from varicella pneumonia), with pregnant women and those with depressed immune systems being more at risk. Pregnant women not known to be immune and who come into contact with chickenpox may need urgent treatment as the virus can cause serious problems for the fetus.

Later in life, viruses remaining dormant in the nerves can reactivate causing localised eruptions of shingles. This occurs particularly in people with compromised immune systems,

such as the elderly, and perhaps even those suffering sunburn. Unlike chickenpox which normally fully settles, shingles may result in persisting post-herpetic neuralgia pain.

A chickenpox vaccine has been available since 1995, and is now required in some countries for children to be admitted into elementary school unless the parent/guardian submits an exemption. In addition, effective medications (e.g. aciclovir) are available to treat chickenpox in healthy adults and immunocompromised persons.

Symptoms and signs

Chickenpox is highly infectious and spreads from person to person by direct contact or through the air from an infected person's coughing or sneezing. Touching the fluid from a chickenpox blister can also spread the disease. A person with chickenpox is contagious 1–2 days before the rash appears and until all blisters have formed scabs. This may take between 5–10 days.[1] It takes from 10–21 days after contact with an infected person for someone to develop chickenpox.[2]

The chickenpox lesions (blisters) start as a 2–4 mm red papule which develops an irregular outline (rose petal). A thin-walled, clear vesicle (dew drop) develops on top of the area of redness. This "dew drop on a rose petal" lesion is very characteristic for chickenpox. After about 8–12 hours the fluid in the vesicle gets cloudy and the vesicle breaks leaving a crust. The fluid is highly contagious, but once the lesion crusts over, it is not considered contagious. The crust usually falls off after 7 days sometimes leaving a crater-like scar. Although one lesion goes through this complete cycle in about 7 days, another hallmark of chickenpox is the fact that new lesions crop up every day for several days. Therefore, it may take about a week until new lesions stop appearing and existing lesions crust over. Children are not sent back to school until all lesions have crusted over.[3]

Second infections with chickenpox occur in immunocompetent individuals, but are uncommon. Such second infections are rarely severe. A soundly-based conjecture being carefully assessed in countries with low prevalence of chickenpox due to immunisation, low birth rates, and increased separation is that immunity has been reinforced by subclinical challenges and this is now less common. This is more dangerous with shingles. There have been reported cases of repeat infections.[4][5]

Congenital defects in babies

These may occur if the child's mother was exposed to VZV during pregnancy. Effects to the fetus may be minimal in nature but physical deformities range in severity from under developed toes and fingers, to severe anal and bladder malformation. Possible problems include:

- Damage to brain: encephalitis, microcephaly, hydrocephaly, aplasia of brain
- Damage to the eye (optic stalk, optic cup, and lens vesicles), microphthalmia, cataracts, chorioretinitis, optic atrophy.

- Other neurological disorder: damage to cervical and lumbosacral spinal cord, motor/sensory deficits, absent deep tendon reflexes, anisocoria/Horner's syndrome
- Damage to body: hypoplasia of upper/lower extremities, anal and bladder sphincter dysfunction
- Skin disorders: zig zag (cicatricial) skin lesions, hypopigmentation

Prognosis and treatment

Chickenpox infection tends to be milder the younger a child is and symptomatic treatment for itch (e.g. calamine lotion and/or antihistamines) and fever (with paracetamol or ibuprofen) is usually all that is required. Infection in otherwise healthy adults tends to more severe and active; treatment with antiviral drugs (e.g. aciclovir) is generally advised. Patients of any age with depressed immune systems or extensive eczema are at risk of more severe disease and should also be treated with antiviral medication. In the U.S., 55 percent of chickenpox deaths were in the over-20 age group.

Screening and prevention

In the UK Varicella antibodies are measured as part of the routine of prenatal care, and by 2005 all NHS healthcare personnel had determined their immunity and been immunised if they were non-immune and have direct patient contact.

History

One history of medicine book credits Giovanni Filippo (1510–1580) of Palermo with the first description of varicella (chickenpox). Subsequently in the 1600s, an English physician named Richard Morton described what he thought a mild form of smallpox as "chicken pox." Later, in 1767, a physician named William Heberden, also from England, was the first physician to clearly demonstrate that chickenpox was different from smallpox. However, it is believed the name chickenpox was commonly used in earlier centuries before doctors identified the disease.

There are many explanations offered for the origin of the name chickenpox:

- the specks that appear looked as though the skin was pecked by chickens;
- the disease was named after chick peas, from a supposed similarity in size of the seed to the lesions;
- Samuel Johnson suggested that the disease was "no very great danger," thus a "chicken" version of the pox;
- the term reflects a corruption of the Old English word, "giccin", which meant "itching".

As "pox" also means curse, in medieval times some believed it was a plague brought on to curse children by the use of black magic.

During the medieval era, oatmeal was discovered to soothe the sores, and oatmeal baths are today still commonly given to relieve itching.

Vaccination

Japan was among the first countries to routinely vaccinate for chickenpox. Routine vaccination against varicella zoster virus is also performed in the United States, and the incidence of chickenpox has been dramatically reduced there (from 4 million cases per year in the pre-vaccine era to approximately 400,000 cases per year as of 2005). In Europe most countries do not currently vaccinate against varicella, though the vaccine is gaining wider acceptance. Australia, Canada, and other countries have now adopted recommendations for routine immunization of children and susceptible adults against chickenpox. Other countries, such as Germany and the United Kingdom, have targeted recommendations for the vaccine, e.g., for susceptible health care workers at risk of varicella exposure.

Chickenpox is most often a mild disease, especially for children. Prior to the introduction of vaccine, there were around 4,000,000 cases per year in the U.S., mostly children, with typically 100 or fewer deaths. Though mostly children caught it, the majority of deaths (by as much as 80%) were among adults. Additionally, chickenpox involved the hospitalization of about 10,000 people each year.[6]

During 2003 and the first half of 2004, the CDC reported eight deaths from varicella, six of whom were children or adolescents. These deaths and hospitalizations have substantially declined in the U.S. due to vaccination,[7][8] though the rate of shingles infection has increased for the same reason. The vaccine has more recently been determined to be effective at preventing shingles (zoster) in persons 60 years of age and older, if administered regularly.[9]

The long-term duration of protection from varicella vaccine is unknown, but there are now persons vaccinated more than thirty years ago with no evidence of waning immunity, while others have become vulnerable in as few as 6 years. Assessments of duration of immunity are complicated in an environment where natural disease is still common, which typically leads to an overestimation of effectiveness, and we are only now entering an era in the U.S. where the long-term efficacy of varicella vaccine can be accurately gauged.[10]

The vaccine is exceedingly safe: approximately 5% of children who receive the vaccine develop a fever or rash, but there have been no deaths yet (as of 1 May 2006) attributable to the vaccine despite more than 40 million doses being administered.[11] Cases of vaccine-related chicken pox have been reported in patients with a weakened immune system,[11][12] but no deaths.

The literature contains several reports of adverse reactions following varicella vaccination,[13][14][15][16][17][18][19][20][21][22][23][24][25] including vaccine-strain zoster in children and adults.[26][27] A mean of 2,350 reports per year are attributed to varicella vaccine based on 20,004 cases reported to the Vaccine Adverse Event Reporting System (VAERS) database from May, 1995 through December, 2003. Minor events are known to be under-reported to VAERS.

Controversy

Mortality due to primary varicella has declined significantly in countries which make wide use of the varicella vaccine.[7][11] Zoster (shingles) occurs decades after varicella and unsurprisingly zoster incidence has not declined in multiple studies. It is too early to observe the effect on postherpetic neuralgia (PHN).

It has been claimed that shingles may increase after introduction of varicella vaccine.[28][29] There is yet no evidence this has occurred, and it might occur in the absence of immunisation due to a general decrease in childhood infection for other reasons.[30]

Vaccination is common in the United States, with 41 of the 50 states require immunization for children attending government-run schools. All 50 states offer a medical exemption, and 48 of those states also offering philosophical and/or religious exemptions. The vaccination is not routine in the United Kingdom. Debate continues in the UK on the time when it will be desirable to adopt routine chickenpox vaccination, and in the U.S. opinions that it should be dropped, individually, or along with all immunizations, are also voiced.

Additional controversy has arisen because cell lines derived from aborted fetal tissue were used in its development, and thus violates the ethics and beliefs of people who oppose the use of aborted fetal tissue in medical research.CDC

Duration of immunity

Some vaccinated children have been found to lose their protective antibody in as little as five to eight years; however, according to the World Health Organization: "After observation of study populations for periods of up to 20 years in Japan and 10 years in the United States, more than 90% of immunocompetent persons who were vaccinated as children were still protected from varicella."[6] As time goes on, boosters may be determined to be necessary, and introduced. Persons infected after vaccine experience milder cases of chicken pox.[2]

Catching wild chickenpox as a child has been thought to commonly result in lifelong immunity, indeed parents have deliberately ensured this in the past with "pox parties" (and similarly for some other diseases such as rubella. See below.) Historically, exposure of adults to contagious children has boosted their immunity, reducing the risk of shingles.[29] Second episodes of chickenpox have been rare, but occur and probably more frequently in the UK latterly and definitely more frequently in the vaccine group. In one study, 30% of children had lost the antibody after five years, and 8% had already caught "wild" chickenpox in that five year period.[31]

The CDC and corresponding national organisations are carefully observing the failure rate which may be high compared with other modern vaccines - large outbreaks of chickenpox having occurred at schools which required their children to be vaccinated.

Immunocompromise

The mortality rate in immunocompromised patients with disseminated herpes zoster is 5-15%, with most deaths from pneumonia. Vaccines, unfortunately are less effective among these high-risk patients, as well as being more dangerous because it is an attenuated live virus (see last footnote), but clearly immunisation before immunocompromise would be desirable.

Pox parties

A "pox party" is a party held by parents for the purpose of infecting their children with childhood diseases. Similar ideas have applied to other diseases, e.g. measles, but are now discouraged by doctors and health services. The rationale behind such parties is that guests exposed to the varicella virus will contract the disease and develop strong and persistent immunity, at an age before disaster is likely particularly from chickenpox or rubella.

The first reference to such a practice is the letter of Lady Montagu to Sarah Chiswell describing the parties people in Istanbul made for the purpose of variolation - an effective technique for gaining immunity to smallpox, which she imported to England.

Pox parties have been portrayed in TV cartoons, including South Park ("Chickenpox") and The Simpsons ("Milhouse of Sand and Fog").

See also

- Vaccine controversy

Notes

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Flu vaccine

The *flu vaccine* is a vaccine to protect against the highly variable influenza virus.

The annual flu kills an estimated 36,000 people in the United States each year. The annually updated trivalent flu vaccine for the 2006-2007 season consists of hemagglutinin (HA) surface glycoprotein components from influenza H3N2, H1N1, and B influenza viruses.[1]

Each year the influenza virus changes and different strains become dominant. Due to the high mutability of the virus a particular vaccine formulation usually only works for about a year. The World Health Organization co-ordinates the contents of the vaccine each year to contain the most likely strains of the virus to attack the next year. The flu vaccine is usually recommended for anyone in a high-risk group who would be likely to suffer complications from influenza.

History of the flu vaccine

Vaccines are used in both humans and nonhumans. Human vaccine is meant unless specifically identified as a veterinary or poultry or livestock vaccine.

Vaccines prior to flu vaccines

A vaccine is an antigenic preparation used to produce active immunity to a disease, in order to prevent or ameliorate the effects of infection by any natural or "wild" strain of the organism. The process of distributing and administrating vaccines is referred to as vaccination. Smallpox is the first disease people tried to prevent by purposely inoculating themselves with other types of infections. Smallpox inoculation is believed to have started in India or China before 200 BC. In 1718, Lady Mary Wortley Montague reported that the Turks have a habit of deliberately inoculating themselves with fluid taken from mild cases of smallpox and she inoculated her own children. In 1796 Edward Jenner inoculated using cowpox (a mild relative of the deadly smallpox virus). Pasteur and others built on this.[2]

Influenza

Influenza commonly known as the flu, is an infectious disease that infects birds and mammals (primarily of the upper airways and lungs in mammals) and is caused by an RNA virus of the Orthomyxoviridae family (the influenza viruses). The most common and characteristic symptoms of influenza in humans are fever, pharyngitis (sore throat), myalgia (muscle pains), severe headache, coughing, and malaise (weakness and fatigue).[3] Hippocrates first described the symptoms of influenza in 412 B.C.. Since then, the virus has undergone mutations and shifts and has caused numerous pandemics. The first influenza pandemic was recorded in 1580, since this time, various methods have been employed to eradicate its cause.[4] The etiological cause of influenza, the orthomyxoviridae was finally discovered by the Medical Research Council (MRC) of the United Kingdom in 1933.[5]

Known flu pandemics:[6]

- 1889-90 - Asiatic (Russian) Flu, mortality rate said to be 0.75-1 death per 1000 possibly H2N2

1900 - possibly H3N8
1918–20 – Spanish Flu, 500 million ill, at least 40 million died of H1N1
1957–58 – Asian Flu, 1 to 1.5 million died of H2N2
1968–69 – Hong Kong Flu, 3/4 to 1 million died of H3N2

Flu vaccine origins

In the world wide Spanish flu pandemic of 1918, "Physicians tried everything they knew, everything they had ever heard of, from the ancient art of bleeding patients, to administering oxygen, to developing new vaccines and sera (chiefly against what we now call Hemophilus influenzae—a name derived from the fact that it was originally considered the etiological agent—and several types of pneumococci). Only one therapeutic measure, transfusing blood from recovered patients to new victims, showed any hint of success."[7]

"In 1931, viral growth in embryonated hens' eggs was discovered, and in the 1940s, the US military developed the first approved inactivated vaccines for influenza, which were used in the Second World War".[2]

Flu vaccine acceptance

The current egg-based technology for producing influenza vaccine was created in the 1950s.[8]

"The WHO Global Influenza Surveillance Network was established in 1952. The network comprises 4 WHO Collaborating Centres (WHO CCs) and 112 institutions in 83 countries, which are recognized by WHO as WHO National Influenza Centres (NICs). These NICs collect specimens in their country, perform primary virus isolation and preliminary antigenic characterization. They ship newly isolated strains to WHO CCs for high level antigenic and genetic analysis, the result of which forms the basis for WHO recommendations on the composition of influenza vaccine for the Northern and Southern Hemisphere each year."[9]

In the U.S. swine flu scare of 1976 President Gerald Ford was confronted with a potential swine flu pandemic. The vaccination program was plagued by delays and public relations problems, but about 24% of the population was vaccinated by the time the program was cancelled with much concern and doubt about flu vaccination.[10]

According to the CDC: "Influenza vaccination is the primary method for preventing influenza and its severe complications. [...] Vaccination is associated with reductions in influenza-related respiratory illness and physician visits among all age groups, hospitalization and death among persons at high risk, otitis media among children, and work absenteeism among adults. Although influenza vaccination levels increased substantially during the 1990s, further improvements in vaccine coverage levels are needed".[11]

Current status

"Vaccination in the veterinary world pursues four goals: (i) protection from clinical disease, (ii) protection from infection with virulent virus, (iii) protection from virus excretion, and (iv) serological differentiation of infected from vaccinated animals (so-called DIVA principle). In the field of influenza vaccination, neither commercially available nor experimentally tested vaccines have been shown so far to fulfil all of these requirements."[12]

Flu research includes molecular virology, molecular evolution, pathogenesis, host immune responses, genomics, and epidemiology. These help in developing influenza countermeasures such as vaccines, therapies and diagnostic tools. Improved influenza countermeasures require basic research on how viruses enter cells, replicate, mutate, evolve into new strains and induce an immune response. The Influenza Genome Sequencing Project is creating a library of influenza sequences that will help us understand what makes one strain more lethal than another, what genetic determinants most affect immunogenicity, and how the virus evolves over time. Solutions to limitations in current vaccine methods are being researched.

"Today, we have the capability to produce 300 million doses of trivalent vaccine per year - enough for current epidemics in the Western world, but insufficient for coping with a pandemic."[2][13]

Clinical trials of vaccines

A vaccine is assessed in terms of the reduction of the risk of disease produced by vaccination, its efficacy. In contrast, in the field, the effectiveness of a vaccine is the practical reduction in risk for an individual when they are vaccinated under real-world conditions.[14] Measuring efficacy of influenza vaccines is relatively simple, as the immune response produced by the vaccine can be assessed in animal models, or the amount of antibody produced in vaccinated people can be measured,[15] or most rigorously, by immunising adult volunteers and then challenging with virulent influenza virus.[16] In studies such as these, influenza vaccines showed high efficacy and produced a protective immune response. For ethical reasons, such challenge studies cannot be performed in the population most at risk from influenza - the elderly and young children. However, studies on the effectiveness of flu vaccines in the real world are uniquely difficult. The vaccine may not be matched to the virus in circulation, virus prevalence varies widely between years and influenza is often confused with other flu-like illnesses.[17]

Nevertheless, multiple clinical trials of both live and inactivated influenza vaccines have been performed and their results pooled and analyzed in several recent meta-analyzes. Studies on live vaccines have very limited data, but these preparations may be more effective than inactivated vaccines.[16] The meta-analyses examined the efficacy and effectiveness of inactivated vaccines in adults,[18] children,[19] and the elderly.[20][21] In adults, vaccines show high efficacy against the targeted strains, but low effectiveness overall, so the benefits of vaccination are small, with a one-quarter reduction in risk of contracting influenza but no effect on the rate of hospitalization.[18] In children, vaccines again showed high efficacy, but low effectiveness in preventing "flu-like illness", in children under two the data are extremely limited, but vaccination appeared to confer no measurable benefit.[19] In the elderly, vaccination does not reduce the frequency of influenza, but may reduce pneumonia, hospital admission and deaths from influenza or pneumonia.[20][21] The measured effectiveness of the vaccine in the elderly varies depending on whether the population studies is in residential care homes, or in the community, with the vaccine appearing more effective in an institutional environment. This apparent effect may be due to selection bias or differences in diagnosis and surveillance.

Overall, the benefit of influenza vaccination is clearest in the elderly, with vaccination in children of questionable benefit. Vaccination of adults is not predicted to produce significant improvements in public health. The apparent contradiction between vaccines with high efficacy, but low effectiveness, may reflect the difficulty in diagnosing influenza under clinical conditions and the large number of strains circulating in the population.[17]

Who should get it

Yearly influenza vaccination should be routinely offered to patients at risk of complications of influenza:

- the elderly (UK recommendation is those aged 65 or above)
- patients with chronic lung diseases (asthma, COPD, etc.)
- patients with chronic heart diseases (congenital heart disease, chronic heart failure, ischaemic heart disease)
- patients with chronic liver diseases (including liver cirrhosis)

- patients who are immunosuppressed (those with HIV or who are receiving drugs to suppress the immune system such as chemotherapy and long-term steroids) and their household contacts
- healthcare workers (both to prevent sickness and to prevent spread to patients)[22]

The only contraindication is known anaphylaxis to the vaccine or its component.

In the United States a person aged 50-64 is nearly ten times more likely to die an influenza-associated death as a person under age 50 and a person over age 65 is over ten times more likely to die an influenza-associated death as a person in the 50-64 age group.[23] Vaccination of those over age 65 reduces influenza-associated death by about 50%.[24][25] However, it is unlikely that the vaccine completely explains the results since elderly people who get the vaccine are likely more healthy and health-conscious than those who don't.[26]

Flu vaccine virus selection

Selecting viruses for the vaccine manufacturing process is very difficult.

At the U.S.'s Food and Drug Administration's (FDA) Center for Biologics Evaluation and Research's Vaccines and Related Biological Products Advisory Committee's 101st meeting of February 16, 2005, an extensive discussion and vote was held concerning next year's flu vaccine virus selection; but began with a summary of the previous year:

Influenza B

"For Influenza B, the question was asked: are there new strains present? And the answer was yes, and in 2004, the majority of the viruses were similar to a strain called B/Shanghai/361/2002, which is from the so-called B/Yamagata/1688 hemagglutinin lineage. That lineage was not the one that was being used in the vaccine that was current last year. In a minority of the strains that were found during the epidemiologic studies were similar to the strain that was in the vaccine for last year, which was B/Hong Kong/330/2001, which belongs to the HA lineage that we represent with the strain B/Victoria/287. In answer to the question were these new viruses spreading, the answer, of course, is definitely yes. The Fujian-like viruses had become widespread around the world and were predominant everywhere, and these B/Shanghai-like strains at the time we were holding this meeting in February were predominant not only in North America and the United States, but also in Asia and Europe."

New viruses

"Were the new viruses that were identified and spreading, were those inhibited by the current vaccines? And this question, as it sometimes is, was not a very definite no or yes. It was a little bit difficult to interpret, but it seemed like many of the A/Fujian-like viruses were not well inhibited by the current vaccines, although some of them were. For the B/Shanghai-like strains, of course, we've known for a long time that these two divergent hemagglutinin lineages are not that well inhibited one by the other, and as time has gone on and antigenic drift has occurred in these strains, that has become truer. Generally we also know that for the B/Yamagata-like strains and the B/Victoria-like strains, that very young children and people who haven't been immunologically primed, exposure to one of these does not seem to immediately give antibodies that cross-react with the other HA lineage."

Manufacturing issues

"So were there strains that were suitable for manufacturing? And the answer was yes. Of course, we all know that for inactivated vaccines and for live attenuated vaccines manufacturing depends on having egg adapted strains, either the wild-type or reassortant, and in the case of the live vaccine, of course, it has to be a reassortant for the attenuation phenotype. But there were A/Fujian-like strains that were available, and there was a high growth reassortant that was being used in manufacturing for the Southern Hemisphere

already, the A/Wyoming/3/2003 X 147 reassortant. For the B strain, there were a number of wild-type isolates that seemed to be suitable for manufacturing, including B/Jilin/20/2003 and B/Jiangsu/10/2003, in addition to the B/Shanghai/361 strain itself."

Strains selected

"So based on that, the strains that were selected for this year include A/New Caledonia/20/99-like strain, which in this case really is A/New Caledonia/20/99. For the B/Shanghai/361/2002-like recommendation that was made, there were all three of these strains, B/Shanghai, B/Jilin, and B/Jiangsu. And for the A/Fujian/411/2002-like recommendation that was made and the A/Wyoming/3/2003 strain was chosen or is the one that has become widely used for vaccine preparation. Now, the implications of the strain selection were that preparation of the vaccines was on schedule throughout the year. All of the strains seemed to be typical and easy to adapt for manufacturing purposes, and going into the summer, the supply of vaccine was expected to match the demand predicted by previous years' experiences."

Unexpected difficulties

"But what happened was that we ended up with a vaccine shortage at the end of the summer, and just to try to put that into a little perspective, from January until August, manufacturing had been progressing on schedule even including these two new strains that were recommended for use in vaccines, and it was anticipated there were going to be about 100 million doses of vaccine from all of the manufacturers combined for this year. In August of 2004, Chiron notified regulatory authorities about a sterility issue and indicated that investigation to identify the cause and the implementation of corrections was underway, and at that time Chiron made a public announcement indicating that there would be a possible delay in distribution and possibly a reduction in the amount of vaccine that would be available. You also probably all know that in early October of 2004, the MHRA, the UK regulatory authority, announced that they were suspending Chiron's license to manufacture inactivated influenza vaccine for three months, and that was based on the issues that have previously been identified and were in investigation and correction by Chiron. Subsequently, over the next few weeks and certainly by November of 2004, it became clear after consultation between FDA and MHRA that the vaccine that Chiron had planned to make was not going to be available for us in the United States."

Response to unexpected difficulties

"In response to that, there were a number of things that happened within the Public Health Service, and I'll just very briefly indicate some of those. At FDA there was a lot of work done to evaluate manufacturers who were not licensed in the United States to identify whether their vaccines could be used under IND. There was consultation with manufacturers to discuss regulatory mechanisms going forward from this time for getting approval of new products in the United States. That includes accelerated approval, fast track and priority

reviews to facilitate those new licenses, and all of these things actually have been continuing."[27]

Flu vaccine manufacturing

Flu vaccines are available both as an injection of killed virus and as nasal spray of live attenuated influenza virus (LAIV) (sold as FluMist). Clinical trials suggest that the live virus may be more effective at preventing infection, but FluMist has not been approved in the United States for use in children younger than 5.[28]

Flu vaccine is usually grown in fertilized chicken eggs. Both types of flu vaccines are contraindicated for those with severe allergies to egg proteins and people with a history of Guillain-Barré syndrome.[29]

On October 5, 2004, Chiron Corporation, a corporation contracted to deliver half of the expected flu vaccine for the United States and a significant portion to the UK, issued a press release[30] that stated it was unable to dispense its stock for the 2004-2005 season, due to suspension of the corporation's license to produce the vaccine by the Medicines and Healthcare Products Regulatory Agency. However, the Centers for Disease Control and Prevention took action to enlist the help of other companies such as MedImmune and Aventis Pasteur to supply vaccine in high-risk populations in the United States.

H5N1

WHO pandemic phases

1. Low risk
2. New virus
3. Self limiting
4. Person to person
5. Epidemic exists
6. Pandemic exists

There are several H5N1 vaccines for several of the avian H5N1 varieties, some for use in humans and some for use in poultry. H5N1 continually mutates, meaning vaccines based on current samples of avian H5N1 cannot be depended upon to work in the case of a future pandemic of H5N1. While there can be some cross-protection against related flu strains, the best protection would be from a vaccine specifically produced for any future pandemic flu virus strain. Dr. Daniel Lucey, co-director of the Biohazardous Threats and Emerging Diseases graduate program at Georgetown University has made this point, "There is no H5N1 pandemic so there can be no pandemic vaccine." However, "pre-pandemic vaccines" have been created; are being refined and tested; and do have some promise both in furthering research and preparedness for the next pandemic. Vaccine manufacturing companies are being encouraged to increase capacity so that if a pandemic vaccine is needed, facilities will be available for rapid production of large amounts of a vaccine specific to a new pandemic strain.

Problems with H5N1 vaccine production include:

- lack of overall production capacity

- lack of surge production capacity (it is impractical to develop a system that depends on hundreds of millions of 11-day old specialized eggs on a standby basis)
- the pandemic H5N1 might be lethal to chickens

Cell culture (cell-based) manufacturing technology can be applied to influenza vaccines as they are with most viral vaccines and thereby solve the problems associated with creating flu vaccines using chicken eggs as is currently done.[31][32] The US government has purchased from Sanofi Pasteur and Chiron Corporation several million doses of vaccine meant to be used in case of an influenza pandemic of H5N1 avian influenza and is conducting clinical trials with these vaccines.[33] Researchers at the University of Pittsburgh have had success with a genetically engineered vaccine that took only a month to make and completely protected chickens from the highly pathogenic H5N1 virus.[34]

According to the United States Department of Health & Human Services:

In addition to supporting basic research on cell-based influenza vaccine development, HHS is currently supporting a number of vaccine manufacturers in the advanced development of cell-based influenza vaccines with the goal of developing U.S.-licensed cell-based influenza vaccines produced in the United States. Dose-sparing technologies. Current U.S.-licensed vaccines stimulate an immune response based on the quantity of HA (hemagglutinin) antigen included in the dose. Methods to stimulate a strong immune response using less HA antigen are being studied in H5N1 and H9N2 vaccine trials. These include changing the mode of delivery from intramuscular to intradermal and the addition of immune-enhancing adjuvant to the vaccine formulation. Additionally, HHS is soliciting contract proposals from manufacturers of vaccines, adjuvants, and medical devices for the development and licensure of influenza vaccines that will provide dose-sparing alternative strategies.[35]

Chiron Corporation is now recertified and under contract with the National Institutes of Health to produce 8,000-10,000 investigational doses of Avian Flu (H5N1) vaccine. MedImmune and Aventis Pasteur are under similar contracts.[36] The United States government hopes to obtain enough vaccine in 2006 to treat 4 million people. However, it is unclear whether this vaccine would be effective against a hypothetical mutated strain that would be easily transmitted through human populations, and the shelflife of stockpiled doses has yet to be determined.[37]

The New England Journal of Medicine reported on March 30, 2006 on one of dozens of vaccine studies currently being conducted. The Treanor et al. study was on vaccine produced from the human isolate (A/Vietnam/1203/2004 H5N1) of a virulent clade 1 influenza A (H5N1) virus with the use of a plasmid rescue system, with only the hemagglutinin and neuraminidase genes expressed and administered without adjuvant. "The rest of the genes were derived from an avirulent egg-adapted influenza A/PR/8/34 strain. The hemagglutinin gene was further modified to replace six basic amino acids associated with high pathogenicity in birds at the cleavage site between hemagglutinin 1 and hemagglutinin 2. Immunogenicity was assessed by microneutralization and hemagglutination-inhibition assays with the use of the vaccine virus, although a subgroup of samples were tested with the use of the wild-type influenza A/Vietnam/1203/2004 (H5N1) virus." The results of this study combined with others scheduled to be completed by Spring 2007 is hoped will provide

a highly immunogenic vaccine that is cross-protective against heterologous influenza strains.[38]

On August 18, 2006. the World Health Organization changed the H5N1 strains recommended for candidate vaccines for the first time since 2004. "The WHO's new prototype strains, prepared by reverse genetics, include three new H5N1 subclades. The hemagglutinin sequences of most of the H5N1 avian influenza viruses circulating in the past few years fall into two genetic groups, or clades. Clade 1 includes human and bird isolates from Vietnam, Thailand, and Cambodia and bird isolates from Laos and Malaysia. Clade 2 viruses were first identified in bird isolates from China, Indonesia, Japan, and South Korea before spreading westward to the Middle East, Europe, and Africa. The clade 2 viruses have been primarily responsible for human H5N1 infections that have occurred during late 2005 and 2006, according to WHO. Genetic analysis has identified six subclades of clade 2, three of which have a distinct geographic distribution and have been implicated in human infections:

- Subclade 1, Indonesia
- Subclade 2, Middle East, Europe, and Africa
- Subclade 3, China

On the basis of the three subclades, the WHO is offering companies and other groups that are interested in pandemic vaccine development these three new prototype strains:

- An A/Indonesia/2/2005-like virus
- An A/Bar headed goose/Quinghai/1A/2005-like virus
- An A/Anhui/1/2005-like virus

[...] Until now, researchers have been working on prepandemic vaccines for H5N1 viruses in clade 1. In March, the first clinical trial of a US vaccine for H5N1 showed modest results. In May, French researchers showed somewhat better results in a clinical trial of an H5N1 vaccine that included an adjuvant. Vaccine experts aren't sure if a vaccine effective against known H5N1 viral strains would be effective against future strains. Although the new viruses will now be available for vaccine research, WHO said clinical trials using the clade 1 viruses should continue as an essential step in pandemic preparedness, because the trials yield useful information on priming, cross-reactivity, and cross-protection by vaccine viruses from different clades and subclades."[39][40]

Flu seasons

2003-2004 season

The production of flu vaccine requires a lead time of about six months before the season. It is possible that by flu season a strain becomes common for which the vaccine does not provide protection. In the 2003-2004 season the vaccine was produced to protect against A/Panama, A/New Caledonia, and B/Hong Kong. A new strain, A/Fujian, was discovered after production of the vaccine started and vaccination gave only partial protection against this strain.

Nature magazine reported that the Influenza Genome Sequencing Project, using phylogenetic analysis of 156 H3N2 genomes, "explains the appearance, during the 2003–

2004 season, of the 'Fujian/411/2002'-like strain, for which the existing vaccine had limited effectiveness" as due to an epidemiologically significant reassortment. "Through a reassortment event, a minor clade provided the haemagglutinin gene that later became part of the dominant strain after the 2002–2003 season. Two of our samples, A/New York/269/2003 (H3N2) and A/New York/32/2003 (H3N2), show that this minor clade continued to circulate in the 2003–2004 season, when most other isolates were reassortants."[41]

According to the CDC:

During the 2003-2004 influenza season, influenza A (H1), A (H3N2), and B viruses co-circulated worldwide, and influenza A (H3N2) viruses predominated. Several Asian countries reported widespread outbreaks of avian influenza A (H5N1) among poultry. In Vietnam and Thailand, these outbreaks were associated with severe illnesses and deaths among humans. In the United States, the 2003-2004 influenza season began earlier than most seasons, peaked in December, was moderately severe in terms of its impact on mortality, and was associated predominantly with influenza A (H3N2) viruses.[42]

During September 28, 2003 - May 22, 2004, WHO and NREVSS collaborating laboratories in the United States tested 130,577 respiratory specimens for influenza viruses; 24,649 (18.9%) were positive. Of these, 24,393 (99.0%) were influenza A viruses, and 249 (1.0%) were influenza B viruses. Among the influenza A viruses, 7,191 (29.5%) were subtyped; 7,189 (99.9%) were influenza A (H3N2) viruses, and two (0.1%) were influenza A (H1) viruses. The proportion of specimens testing positive for influenza first increased to >10% during the week ending October 25, 2003 (week 43), peaked at 35.2% during the week ending November 29 (week 48), and declined to <10% during the week ending January 17, 2004 (week 2). The peak percentage of specimens testing positive for influenza during the previous four seasons had ranged from 23% to 31% and peaked during late December to late February.[42]

As of June 15, 2004, CDC had antigenically characterized 1,024 influenza viruses collected by U.S. laboratories since October 1, 2003: 949 influenza A (H3N2) viruses, three influenza A (H1) viruses, one influenza A (H7N2) virus, and 71 influenza B viruses. Of the 949 influenza A (H3N2) isolates characterized, 106 (11.2%) were similar antigenically to the vaccine strain A/Panama/2007/99 (H3N2), and 843 (88.8%) were similar to the drift variant, A/Fujian/411/2002 (H3N2). Of the three A (H1) isolates that were characterized, two were H1N1 viruses, and one was an H1N2 virus. The hemagglutinin proteins of the influenza A (H1) viruses were similar antigenically to the hemagglutinin of the vaccine strain A/New Caledonia/20/99. Of the 71 influenza B isolates that were characterized, 66 (93%) belonged to the B/Yamagata/16/88 lineage and were similar antigenically to B/Sichuan/379/99, and five (7%) belonged to the B/Victoria/2/87 lineage and were similar antigenically to the corresponding vaccine strain B/Hong Kong/330/2001.[42]

H9N2

In December 2003, one confirmed case of avian influenza A (H9N2) virus infection was reported in a child aged 5 years in Hong Kong. The child had fever, cough, and nasal discharge in late November, was hospitalized for 2 days, and fully recovered. The source of this child's H9N2 infection is unknown.[42]

H5N1

During January—March 2004, a total of 34 confirmed human cases of avian influenza A (H5N1) virus infection were reported in Vietnam and Thailand. The cases were associated with severe respiratory illness requiring hospitalization and a case-fatality proportion of 68% (Vietnam: 22 cases, 15 deaths; Thailand: 12 cases, eight deaths). A substantial proportion of the cases were among children and young adults (i.e., persons aged 5—24 years). These cases were associated with widespread outbreaks of highly pathogenic H5N1 influenza among domestic poultry.[42]

H7N3

During March 2004, health authorities in Canada reported two confirmed cases of avian influenza A (H7N3) virus infection in poultry workers who were involved in culling of poultry during outbreaks of highly pathogenic H7N3 on farms in the Fraser River Valley, British Columbia. One patient had unilateral conjunctivitis and nasal discharge, and the other had unilateral conjunctivitis and headache. Both illnesses resolved without hospitalization.[42]

H7N2

During the 2003-2004 influenza season, a case of avian influenza A (H7N2) virus infection was detected in an adult male from New York, who was hospitalized for upper and lower respiratory tract illness in November 2003. Influenza A (H7N2) virus was isolated from a respiratory specimen from the patient, whose acute symptoms resolved. The source of this person's infection is unknown.[42]

2004-2005 season

According to the CDC:

On the basis of antigenic analyses of recently isolated influenza viruses, epidemiologic data, and postvaccination serologic studies in humans, the Food and Drug Administration's Vaccines and Related Biological Products Advisory Committee (VRBPAC) recommended that the 2004—05 trivalent influenza vaccine for the United States contain A/New Caledonia/20/99-like (H1N1), A/Fujian/411/2002-like (H3N2), and B/Shanghai/361/2002-like viruses. Because of the growth properties of the A/Wyoming/3/2003 and B/Jiangsu/10/2003 viruses, U.S. vaccine manufacturers are using these antigenically equivalent strains in the vaccine as the H3N2 and B components, respectively. The A/New Caledonia/20/99 virus will be retained as the H1N1 component of the vaccine.[42]

2005-2006 season

The vaccines produced for the 2005-2006 season use:

- an A/New Caledonia/20/1999-like(H1N1);
- an A/California/7/2004-like(H3N2) (or the antigenically equivalent strain A/New York/55/2004);
- a B/Jiangsu/10/2003-like viruses.

In people in the US, overall flu and pneumonia deaths were below those of a typical flu season with 84% Influenzavirus A and the rest Influenzavirus B. Of the patients who had Type A viruses, 80% had viruses identical or similar to the A bugs in the vaccine. 70% of the people testing positive for a B virus had Type B Victoria, a version not found in the vaccine.[43]

"During the 2005-06 season, influenza A (H3N2) viruses predominated overall, but late in the season influenza B viruses were more frequently isolated than influenza A viruses. Influenza A (H1N1) viruses circulated at low levels throughout the season. Nationally, activity was low from October through early January, increased during February, and peaked in early March. Peak activity was less intense, but activity remained elevated for a longer period of time this season compared to the previous three seasons. The longer period of elevated activity may be due in part to regional differences in the timing of peak activity and intensity of influenza B activity later in the season."[44]

2006-2007 season

The 2006-07 influenza vaccine composition recommended by the World Health Organization on February 15, 2006 and the US FDA's Vaccines and Related Biological Products Advisory Committee (VRBPAC) on February 17, 2006 use:

- an A/New Caledonia/20/99 (H1N1)-like virus;
- an A/Wisconsin/67/2005 (H3N2)-like virus (A/Wisconsin/67/2005 and A/Hiroshima/52/2005 strains);
- a B/Malaysia/2506/2004-like virus from B/Malaysia/2506/2004 and B/Ohio/1/2005 strains which are of B/Victoria/2/87 lineage.[45]

Flu vaccine for nonhumans

Horses with horse flu can run a fever, have a dry hacking cough, have a runny nose, and become depressed and reluctant to eat or drink for several days but usually recover in 2 to 3 weeks. "Vaccination schedules generally require a primary course of 2 doses, 3-6 weeks apart, followed by boosters at 6-12 month intervals. It is generally recognised that in many cases such schedules may not maintain protective levels of antibody and more frequent administration is advised in high-risk situations."[46]

"[P]oultry vaccines, made on the cheap, are not filtered and purified [like human vaccines] to remove bits of bacteria or other viruses. They usually contain whole virus, not just the hemagglutin spike that attaches to cells. Purification is far more expensive than the work in eggs, Dr. Stöhr said; a modest factory for human vaccine costs $100 million, and no veterinary manufacturer is ready to build one. Also, poultry vaccines are "adjuvated" — boosted — with mineral oil, which induces a strong immune reaction but can cause inflammation and abscesses. Chicken vaccinators who have accidentally jabbed themselves have developed painful swollen fingers or even lost thumbs, doctors said. Effectiveness may also be limited. Chicken vaccines are often only vaguely similar to circulating flu strains — some contain an H5N2 strain isolated in Mexico years ago. 'With a chicken, if you use a vaccine that's only 85 percent related, you'll get protection,' Dr. Cardona said. 'In humans,

you can get a single point mutation, and a vaccine that's 99.99 percent related won't protect you.' And they are weaker [than human vaccines]. 'Chickens are smaller and you only need to protect them for six weeks, because that's how long they live till you eat them,' said Dr. John J. Treanor, a vaccine expert at the University of Rochester. Human seasonal flu vaccines contain about 45 micrograms of antigen, while an experimental A(H5N1) vaccine contains 180. Chicken vaccines may contain less than 1 microgram. 'You have to be careful about extrapolating data from poultry to humans,' warned Dr. David E. Swayne, director of the agriculture department's Southeast Poultry Research Laboratory. 'Birds are more closely related to dinosaurs.'"[47]

Researchers, led by Nicholas Savill of the University of Edinburgh in Scotland, used mathematical models to simulate the spread of H5N1 and concluded that "at least 95 per cent of birds need to be protected to prevent the virus spreading silently. In practice, it is difficult to protect more than 90 per cent of a flock; protection levels achieved by a vaccine are usually much lower than this."[48]

See also

- Vaccine for information valid about all vaccines, not just flu vaccines.
- Vaccine controversy for the pros and cons of being vaccinated.

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be met by egg-based vaccine production alone, as it is impractical to develop a system that depends on hundreds of millions of 11-day old specialized eggs on a standby basis. In addition, because a pandemic could result from an avian influenza strain that is lethal to chickens, it is impossible to ensure that eggs will be available to produce vaccine when needed. In contrast, cell culture manufacturing technology can be applied to influenza vaccines as they are with most viral vaccines (e.g., polio vaccine, measles-mumps-rubella vaccine, chickenpox vaccine). In this system, viruses are grown in closed systems such as bioreactors containing large numbers of cells in growth media rather than eggs. The surge capacity afforded by cell-based technology is insensitive to seasons and can be adjusted to vaccine demand, as capacity can be increased or decreased by the number of bioreactors or the volume used within a bioreactor. In addition to supporting basic research on cell-based influenza vaccine development, HHS is currently supporting a number of vaccine manufacturers in the advanced development of cell-based influenza vaccines with the goal of developing U.S.-licensed cell-based influenza vaccines produced in the United States.

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HIV vaccine

An *HIV vaccine* is a hypothetical vaccine against HIV, the etiological agent of AIDS. As there is no known cure for AIDS, the search for a vaccine has become part of the struggle against the disease.

The urgency of the search for a vaccine against HIV stems from the AIDS-related death toll of over 25 million people since 1981.[1] Indeed, in 2002, AIDS became the primary cause of mortality due to an infectious agent in Africa (UNAIDS, 2004).

Alternative medical treatments to a vaccine do exist. Highly active antiretroviral therapy (HAART) has been highly beneficial to many HIV-infected individuals since its introduction in 1996 when the protease inhibitor-based HAART initially became available. HAART allows the stabilisation of the patient's symptoms and viremia, but they do not cure the patient of HIV, nor of the symptoms of AIDS (Martinez-Picardo et al., 2000). And, importantly, HAART does nothing to prevent the spread of HIV through people with undiagnosed HIV infections. Safer sex measures have also proven insufficient to halt the spread of AIDS in the worst affected countries, despite some success in reducing infection rates.

Therefore, a HIV vaccine is generally considered as the most likely, perhaps the only way by which the AIDS pandemic can be halted. However, after over 20 years of research, HIV-1 remains a difficult target for a vaccine.

Difficulties in developing an HIV vaccine

In 1984, after the confirmation of the etiological agent of AIDS by Prof. Robert Gallo, the United States Health and Human Services Secretary Margaret Heckler declared that a vaccine would be available within two years (Associated Press, 1984). However, the classical vaccination approaches that have been successful in the control of various viral diseases by priming the adaptive immunity to recognise the viral envelope proteins have failed in the case of HIV-1, as the epitopes of the viral envelope are too variable. Furthermore, the functionally important epitopes of the gp120 protein are masked by glycosylation,

trimerisation and receptor-induced conformational changes making it difficult to block with neutralising antibodies. In February 2003, Vaxgen announced that their AIDSVAX vaccine was a failure in North America as there was not a statistically significant reduction of HIV infection within the study population (Francis et al., 2003). In November 2003, it also failed clinical trials in Thailand for the same reason. These vaccines both targeted gp120 and were specific for the geographical regions (Billich et al., 2001).

The ineffectiveness of previously developed vaccines primarily stems from two related factors. First, HIV is highly mutable. Because of the virus' ability to rapidly respond to selective pressures imposed by the immune system, the population of virus in an infected individuals typically evolves so that it can evade the two major arms of the adaptive immune system; humoral (antibody-mediated) and systemic (mediated by T cells) immunity. Second, HIV isolates are themselves highly variable. HIV can be categorized into multiple clades and subtypes with a high degree of genetic divergence. Therefore, the immune responses raised by any vaccine need to be broad enough to account for this variability. Any vaccine that lacks this breadth is unlikely to be effective.

The typical animal model for vaccine research is the monkey, often the macaque. The monkeys can be infected with SIV or the chimeric SHIV for research purposes. However, the well-proven route of trying to induce neutralizing antibodies by vaccination has stalled because of the great difficulty in stimulating antibodies that neutralise heterologous primary HIV isolates (Poignard et al., 1999). Some vaccines based on the virus envelope have protected chimpanzees or macaques from homologous virus challenge (Berman et al., 1990), but in clinical trials, individuals who were immunised with similar constructs became infected after later exposure to HIV-1 (Connor et al., 1998).

The human body can defend itself against HIV, as work with monoclonal antibodies (MAb) has proven. That certain individuals can be asymptomatic for decades after infection is encouraging.

Research achievements

Research supports the contention that a safe and effective vaccine is possible. Vaccines against other diseases where correlates were not known and where there were no ideal animal model have been developed.

Most HIV is transmitted heterosexually, which is known to be less efficient than parenteral exposure. Finally, individuals who become infected with HIV do not succumb to the disease for years even in the absence of anti-retroviral therapy, suggesting that the human immune system is capable of controlling HIV infection partially or temporarily.

Enormous effort has been put into understanding how HIV works; it has produced a number of approaches to vaccination, none of which have been effective. Methods attempted include recombinant proteins, synthetic peptides, recombinant viral vectors, recombinant bacterial vectors, recombinant particles, DNA vaccines to induce production of a specific antigen, and whole-killed and live-attenuated HIV, though these latter two have not progressed into clinical trials in uninfected individuals due to an unfavorable benefit/risk ratio. The role of broadly neutralising antibodies (NAb) is under investigation, although earlier results were discouraging. vaccines are used to investigate the HIV glycoproteins. Attacks on particular parts of the RNA code of the virus have shown some promise, such as those against the nef gene which regulates viral replication.

On November 16, 2004, researchers at the French Institut Pasteur announced that they had been able to induce antibodies to significantly block HIV from infecting human cells, an achievement hailed as an important step towards an HIV vaccine. (365gay.com)

On November 29, 2004, Wei Lu, Jean-Marie Andrieu, and colleagues at the University of Paris in France and Pernambuco Federal University in Recife, Brazil, tested a vaccine on 18 Brazilian patients whose T-cell counts stopped dropping after getting three under-the-skin injections of the tailor-made vaccine. Novel Vaccine Stops HIV

On December 1, 2004, Swedish media announced that a new vaccine will be tested on 40 volunteers. If the new method is successful, vaccinations will be performed in Tanzania next year.

On March 13, 2005, China announced it began human trials for an AIDS vaccine. 49 volunteers between the ages of 18 and 50 would receive the vaccine.

On April 14, 2006, Atlanta 12 uninfected volunteers are to start getting the newly developed HIV vaccine.

The burden of HIV-related disease and transmission in Africa demands that enhanced efforts be made to treat large numbers of infected people with antiretroviral drugs, despite the cost and the emergence of resistant strains, while effective preventative vaccines are developed. Also, access to care and the development of simplified monitoring schemes for positive and negative treatment effects, as well as effective planning on how to obtain and distribute HIV vaccines needs to be addressed. This will be an important step if a large scale phase III HIV-vaccine trial is to be effective (WHO-UNAIDS, 2001), as this may bypass what we saw with antiretroviral therapy, that drugs were initially widely used in only developed countries.

Clinical trials to date

17 vaccine candidates are in phase I trials and four in phase I/II. There is only one in phase III (the NIH/Department of Defense's ALVAC vCP 1521 canary pox vector/AIDSVAX prime-boost vaccine trial now under way in Thailand).

Up to May 2000 over 60 phase I/II trials of candidate vaccines had been conducted worldwide. Most initial approaches focused on the HIV envelope protein. At least thirteen different gp120 and gp160 envelope candidates have been evaluated, in the US predominantly through the AIDS Vaccine Evaluation Group. Most research focused on gp120 rather than gp41/gp160, as the latter are generally more difficult to produce and did not initially offer any clear advantage over gp120 forms. Overall, they have been safe and immunogenic in diverse populations, have induced neutralizing antibody in nearly 100% recipients, but rarely induced CD8+ cytotoxic T lymphocytes (CTL). Mammalian derived envelope preparations have been better inducers of neutralizing antibody than candidates produced in yeast and bacteria. Although the vaccination process involved many repeated "booster" injections, it was very difficult to induce and maintain the high anti-gp120 antibody titers necessary to have any hope of neutralizing an HIV exposure.

The availability of several recombinant canarypox vectors has provided interesting results that may prove to be generalizable to other viral vectors. Increasing the complexity of the canarypox vectors by inclusion of more genes/epitopes has increased the percent of volunteers that have detectable CTL to a greater extent than did increasing the dose of the viral vector. Importantly, CTLs from volunteers were able to kill peripheral blood mononuclear cells infected with primary isolates of HIV, suggesting that induced CTLs could have biological significance. In addition, cells from at least some volunteers were able to kill cells infected with HIV from other clades, though the pattern of recognition was not uniform among volunteers. As canarypox is the first candidate HIV vaccine that has induced cross-clade functional CTL responses,

Other strategies that have progressed to phase I trials in uninfected persons include peptides, lipopeptides, DNA, an attenuated Salmonella vector, lipopeptides, p24, etc. Specifically, candidate vaccines that induce one or more of the following are being sought:

- broadly neutralizing antibody against HIV primary isolates;
- cytotoxic T cell responses in a vast majority of recipients;
- strong mucosal immune responses.

On December 13, 2004, a large phase II clinical trial of a novel HIV vaccine began enrolling volunteers at sites in North America, South America, the Caribbean and Australia. The organizers were seeking 3,000 participants. The trial was co-funded by the National Institute of Allergy and Infectious Diseases (NIAID), part of the National Institutes of Health (NIH), and the pharmaceutical company Merck & Co. Inc. Merck developed the experimental vaccine to stimulate HIV-specific cellular immunity, which prompts the body to produce T cells that kill HIV-infected cells. In previous smaller trials, this vaccine was found to be safe and to induce cellular immune responses against HIV in more than half of volunteers.[1]

The Merck vaccine contains a weakened adenovirus that serves as a carrier for three subtype B HIV genes. Subtype B is the most prevalent HIV subtype in the regions of the study sites. Adenoviruses are among the main causes of upper respiratory tract ailments such as

the common cold. Because the vaccine contains only three HIV genes housed in a weakened adenovirus, study participants cannot become infected with HIV or get a respiratory infection from the vaccine.

Organizers expect that it will take approximately one and a half years to fully enroll volunteers into the study. NIAID and Merck expect the trial be completed in four-and-a-half years, with results anticipated in 2009. More information on enrollment can be found at HVTN's Web site.

Novel approaches, including modified vaccinia Ankara (MVA), adeno-associated virus, Venezuelan Equine Encephalitis (VEE) replicons, and codon-optimized DNA have proven to be strong inducers of CTL in macaque models, and have provided at least partial protection in some models. Most of these approaches are, or will soon, enter clinical studies.

Economics of vaccine development

A June 2005 study estimates that $682 million is spent on AIDS vaccine research annually (CITE).

Economic issues with developing an AIDS vaccine include the need for advance purchase commitment (or advance market commitments) because after an AIDS vaccine has been developed, governments and NGOs may be able to bid the price down to marginal cost (CITE).

Conducting trials of HIV vaccines in the countries most affected by the epidemic is a challenge,[76] albeit one that has been successfully met in Thailand. When one or more HIV-1 vaccines is identified, the task will be just beginning. The next step will be ensuring access for populations where the need is the greatest. Currently, over 60 million people have become infected with HIV-1 and hundreds of millions are at risk. Many of these individuals have little access to medical care, no access to adult vaccinations and live in countries where the per capita expenditure on health care is a few dollars.

Often, HIV-1 is ill understood and stigmatized. Diagnostic tests or algorithms may need to be altered. Education will be needed to convey not only the value but the anticipated limitations of the vaccines, so that other preventive strategies will be maintained. The role of community organizations in maintaining this balance will be critical. Regulatory approvals in numerous countries will be required. The issues in the USA are complex.[77] Internationally, there are greater challenges. If a vaccine has not been demonstrated to be universally effective against every HIV-1 subtype, the standard paradigm of approval in one or more industrialized countries followed years or even decades later by acceptance in and distribution to developing countries will not apply. Both the governments of countries affected by HIV-1 and the international regulatory and health authorities must plan ahead for the advent of an HIV-1 vaccine to avoid unnecessary delays.

HIV-1 vaccines might induce antibody responses that would completely prevent HIV-1 infection by strains of virus that are sufficiently well matched to the vaccine. Unfortunately, HIV-1 evolves continuously both within an individual (the source of infection) and within human populations. Therefore, a vaccinated person might be protected initially, but later encounter a virus against which he or she is not immune. Multivalent vaccines or repeated immunization with an updated vaccine may be required for continued protection. Thus, eventually, one might imagine licensure not of a specific HIV-1 vaccine but of a method for

producing the vaccine and its updated versions, somewhat analogous to the annual updates of influenza vaccine.

The scientific challenges involved in discovery of a safe and effective vaccine against HIV-1, although daunting, are only the prelude. The task of developing and deploying a vaccine against HIV-1 will be enormous (i.e. gaining licensure and scaling up to produce vaccine for worldwide distribution, developing distribution methods and establishing purchase mechanisms will require an unprecedented co-operative effort by governments, international agencies, philanthropic organizations and the private sector).[78] Recent recognition of the importance of controlling HIV-1 for public health, economic and political stability has been encouraging and there has been substantial growth in academic, government, nonprofit and pharmaceutical industry vaccine research, but the fight is not over. Stopping the march of the pandemic will conserve economic and human resources needed to care for those already infected. Ending the HIV-1 epidemic is critical to allow economic development and promote political stability in the developing world and to reduce loss of life and suffering worldwide.

Controversy

Reginald Finger, M.D., M.P.H., a member of the Advisory Committee on Immunization Practices (ACIP) in the U.S., has stated that the Committee would have to carefully consider an HIV vaccine's effects on sexual activity.

In an interview with Michael Specter of The New Yorker[2], he said:

"'We would have to look at that closely ... With any vaccine for H.I.V., disinhibition ... would certainly be a factor, and it is something we will have to pay attention to with a great deal of care.'"

Disinhibition is a "medical term for the absence of fear," in this case, fear of sexual activity.

Similar controversy has arisen in response to the recent introduction of the HPV vaccine, which prevents infection with certain strains of human papillomavirus, another sexually transmitted disease.

ACIP is an influential government committee linked to the Centers for Disease Control. ACIP is charged with advising the President on prevention of vaccine-related diseases. Dr. Finger's term expired in June, 2006.

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MMR vaccine

The *MMR vaccine* is a mixture of live attenuated viruses, administered via injection for immunization against measles, mumps and rubella. It is generally administered to children around the age of one year, with a booster dose before starting school (i.e. age 4/5).

It is widely used around the world; since introduction of its earliest versions in the 1970s, over 500 million doses have been used in over 60 countries. As with all vaccinations, long-term effects and efficacy are subject to continuing study. The vaccine is sold by e.g. Merck as M-M-R II[1] and GlaxoSmithKline as Priorix.

Before the widespread use of a vaccine against *measles*, its incidence was so high that patients born before 1949 are assumed to have had measles. Today the incidence of measles has fallen to less than one percent of people under the age of 30 in countries with routine childhood vaccination. Measles has a significant complication rate, which includes pneumonitis and encephalitis.

Studies, such as a Centers for Disease Control (CDC) report on the effect of vaccination against measles in Africa between 1996-2002, have shown that vaccination markedly reduces the mortality rate due to measles.

Mumps is another viral disease of childhood that was once very common. A known but relatively rare complication of mumps is sterility in males.

Rubella, otherwise known as *German measles*, was also very common before the advent of widespread vaccination. The major risk of rubella is if a pregnant woman is infected, her baby may contract congenital rubella from her, which can cause significant congenital defects.

All three diseases are highly contagious.

The MMR vaccine was introduced to induce immunity less painfully than three separate injections at the same time, sooner than at three separate encounters, and more efficiently than either. The incidence and therefore the complications of the three diseases above have declined significantly and this is generally attributed to widespread population vaccination.

Adverse Effects

There are a number of adverse effects listed in the product documentation for the MMR vaccine.[1] Additional side effects and variants are reported including: a rash or slight fever for a few days, one to two weeks after receiving the vaccine, occasionally accompanied by a mild swelling of the salivary glands and some aching or swelling of the joints, respectively from the measles, mumps and rubella components, which have differing incubation periods. They are usually mild and temporary, vanishing within a few days. There are rare reports of more serious adverse effects — only about one in every 100,000 vaccinations is reported to have resulted in a severe adverse effect such as encephalitis or meningitis. Acute disseminated encephalomyelitis is a rare severe adverse effect of the vaccine.

In the UK, the vaccine was the subject of controversy after a 1998 paper by Dr. Andrew Wakefield, which claimed to have found a possible link between MMR and the onset of behavioral abnormalities in children. Numerous peer-reviewed studies have since failed to show any correlation. Since its publication, this conclusion of the study has been retracted by ten of Wakefield's co-authors, and his call for parents to boycott the vaccine in favor of single injections one year apart, has been heavily criticized, both on scientific grounds and for triggering a decline in vaccination rates.[2]

Parents may choose to have each of the three components given separately, but the overwhelming medical opinion is that such spacing of injections does not reduce the chance of adverse effects, but increases the opportunity for infection by the two diseases not immunized against first.

Weighing adverse effects and benefits

While there are recognized effects, rarely serious, from each component of the MMR vaccine, from a public health perspective, the benefit to the population outweighs these concerns. The consensus of medical opinion is that the vaccine is very safe.

Development, Formulation and Administration

The component viral strains of MMR vaccine were developed by propagation in animal cells. The live viruses require animal cells as a host for production of more virus.

For example, in the case of mumps and measles viruses, the virus strains were grown in embryonated hens' eggs and chick embryo cell cultures. This produced strains of virus which

were adapted for the hens egg and less well-suited for human cells. These strains are therefore called attenuated strains. They are sometimes referred to as neuroattenuated because these strains are less virulent to human neurons than the wild strains.[3] [4]

Disease Immunized - Component Vaccine - Virus Strain - Propagation Medium - Growth Medium

Measles - Attenuvax - Enders' attenuated Edmonston strain [5] - chick embryo cell culture - Medium 199

Mumps - Mumpsvax[6] - Jeryl Lynn (B level) strain[7] - chick embryo cell culture - Medium 199

Rubella - Meruvax II - Wistar RA 27/3 strain of live attenuated rubella virus - WI-38 human diploid lung fibroblasts - MEM (solution containing buffered salts, fetal bovine serum, human serum albumin and neomycin, etc.)

The virus is extracted from the human albumin growth medium via the Cohn cold ethanol fractionation method. [1]

MMR II is supplied freeze-dried (lyophilized) and contains live viruses. Before injection it is reconstituted with the solvent provided. It is administered by a subcutaneous injection.

Footnotes

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See also

- ProQuad vaccine

Polio vaccine

Two *polio vaccines* are used throughout the world to combat polio. The first was developed by Jonas Salk, first tested in 1952, and announced to the world by Salk on April 12, 1955. It consists of an injected dose of killed polio virus. Thereafter, Albert Sabin produced an oral polio vaccine using live but weakened (attenuated) virus. Human trials of Sabin's vaccine began in 1957 and it was licensed in 1962.

When the live-virus Sabin oral vaccine was developed, it gained in popularity for several reasons. First, it can 'infect' other, non-vaccinated individuals with whom the vaccinated person has close contact and confer some immunity to them. Second, because the oral vaccine acts in the gut, it confers immunity there and reduces the spread of the wild virus. The injected vaccine, acting through the bloodstream, immunizes the individual but does not reduce the potential for spreading the wild virus. Third, the live-virus oral vaccine is cheaper than the killed-virus vaccine. Finally, the oral vaccine is easier to administer than the injected vaccine, so patients are more likely to complete the immunization series and attain full immunity. Though Salk's vaccine had reduced the incidence of polio to a tiny fraction of what it was in the early 1950s, Sabin's vaccine was considered superior for these reasons and became the standard treatment. The killed-virus vaccine immunized people against the effects of the virus, but the virus could still spread from person to person. It was the live-virus vaccine that enabled the complete eradication of the wild polio virus in the United States.

The major disadvantage of the live-virus vaccine is that it can result in sporadic cases of polio either from the vaccine itself or from the circulation of the vaccine. There is neither risk from the killed-virus vaccine.

In each country, as the incidence of wild polio reaches a very low level, the time comes to change from live vaccine to killed. In the United States the Centers for Disease Control decided this point was reached in 2000 and use of the live-virus vaccine was discontinued. In the UK the change occurred in 2005 and for convenience polio vaccine was combined with Tetanus toxoid and Diphtheria. In states with higher incidence and thus a different relative risk between efficacy and reversion, live vaccine is still used. The live virus also has stringent requirements for transport and storage, which are a problem in some areas.

The two vaccines have eliminated polio from most of the countries in the world and reduced early cases from hundreds of thousands per year to only 1000 worldwide in 2001.

Initial attempts to develop a vaccine were hampered by the difficulty of obtaining enough virus. Growing it in the brains of monkeys produced only small quantities. Rats were used later, but a breakthrough came in 1948, when John Franklin Enders, Thomas Huckle Weller, and Frederick Chapman Robbins developed a method for growing the virus in the laboratory. This breakthrough greatly facilitated vaccine research. Enders and his colleagues were awarded the Nobel Prize in Physiology or Medicine in 1954.

Simian virus contamination

Some medical researchers have expressed fear that rare human cancers may be linked to contamination by the monkey virus SV40 of a proportion of polio vaccines administered in the 1950s and 1960s. Contamination of the vaccines administered to tens of millions of Americans, in both the injected and oral forms, was first discovered in 1961.

Since then, government officials have insisted there is no evidence the simian virus is harmful to humans. But in recent years, dozens of scientific studies have found the virus in a steadily increasing number of rare brain, bone and lung-related tumors. The simian virus has been detected in tumors removed from people never inoculated with the contaminated vaccine, which has raised further concerns.

Vaccine critics assert that the few studies on the cancer-causing effects of SV40 are scientifically flawed, and that health officials have downplayed the potential risks since finding, in 1961, that the contaminant caused tumors in rodents.

Anti-vaccinationists

After the introduction of vaccination in 1796, the first anti-vaccination society was formed in 1798. In the 19th and early 20th centuries, various organizations declared their opposition to vaccination. Until Pasteur and Lister demonstrated the basis of infection and how to prevent it, vaccinations were as dangerous as other surgical treatments of the time. The view of the British government throughout was that vaccination was safer than variolation, and this is not generally disputed; variolation was safer than random infection with smallpox, but potentially spread smallpox infection itself.

The medical community overwhelmingly supports vaccination as an effective and safe way to prevent the spread and reduce the impact of infectious illnesses. Public health advocates overwhelmingly consider that the benefit to the public justifies mandatory programs.

Timeline

After the work of Edward Jenner, vaccination became widespread in the United Kingdom in the early 1800s.[1] Variolation, which had preceded vaccination, was banned in 1840 because of its greater risks. Public policy and successive Vaccination Acts first encouraged vaccination and then made it mandatory, with the highest penalty for refusal being a prison sentence. This was a significant change in the relationship between the British state and its citizens, and there was a public backlash. Initially this was focused against compulsory vaccination, and later included arguments that vaccination was dangerous and ineffective.

In the USA, President Thomas Jefferson took a close interest in vaccination, alongside Dr Waterhouse, chief physician at Boston. Jefferson encouraged the development of ways to transport vaccine material through the Southern states, which included measures to avoid damage by heat, a leading cause of ineffective batches. Smallpox outbreaks were contained by the latter half of the 19th century, a development widely attributed to vaccination of a large portion of the population[2]. Vaccination rates fell after this decline in smallpox cases, and the disease again became epidemic in the 1870s.

Anti-vaccination activity increased again in the USA in the late 19th century. After a visit to New York in 1879 by William Tebb, a prominent British anti-vaccinationist, the Anti-Vaccination Society of America was founded. The New England Anti-Compulsory Vaccination League was formed in 1882, and the Anti-Vaccination League of New York City in 1885.

Arguments against vaccination

The first arguments against vaccination were theological.[3] Some anti-vaccinationists still base their stance against vaccination with reference to the Bible.[4]

In a 2002 paper in the British Medical Journal, two medical historians suggest that the arguments made against the safety and effectiveness of vaccines in the 21st century are similar to those of the early anti-vaccinationists.[5] Another author in the JRSM(2005) describes the differences between contemporary anti-vaccination campaigns and those before 1907.[6]

Anti-vaccinationists argue that:

- Large smallpox epidemics have occurred in highly vaccinated populations, presenting figures from 1905 in the Philippines. Historians note that the Philippine-American War between 1899 and 1913 caused major disruptions to medical facilities, which were noted to damage the effectiveness of vaccines.
- 90% of the decline in infectious disease incidence occurred before the application of specific vaccines.

Even before Pasteur's work on the nature of infection, there was evidence that contagions spread from person to person, even though microscopes were not yet available and the nature of the contagion (microorganisms) could not be elucidated. Subsequently, as demonstrated by Ignaz Semmelweis, Joseph Lister and others, the knowledge that there were specific modes of cross-infection and that these could be avoided diffused through the population. One argument presented by some modern anti-vaccinationists (e.g. Whale.to) is that Pasteur's theory was incorrect and Antoine Bechamp's germ theory[7] better represented the transmission of disease. This view is not widespread, but is not criticised on anti-vaccinationist websites. This view of the genesis of disease provided no rationale for sterilising instruments, and an overlap in those decades between anti-vaccinationist thinking and Bechampist potentially contributed to deaths from infection and cross-infection.

Infection as a complication of vaccination is almost absent in the 20th century in developed countries, but in developing countries re-use of needles has contributed to the spread of HIV. There is an overlap in anti-vaccinationist thought, with the denial both of HIV as the unique causative organism of AIDS and with denial that viruses cause disease. (Viral and bacterial DNA is listed as a dangerous constituent of vaccines by some authors without disagreement visible, from other anti-vaccinationists). These arguments oppose conventional medical arguments that favour expensive public health precautions against HIV infection.

Consequences of success

Success in opposing vaccination, or a particular vaccination, will be reflected in a reduction in use of all or specific vaccinations. If a vaccine is beneficial, then such success will lead to harm; if a vaccine is harmful, then such success will lead to benefit.

The arguments over which of these occurred were considerable even in the 19th century with only a single vaccination to consider - smallpox. After the Royal Commission, which reported in considerable detail, the Royal Statistical Society devoted a meeting to considering the statistical aspects of the argument. The Royal Commission concluded that smallpox vaccination was effective.

From 1796 to 1905, large changes in English society added to the difficulties of analysis. In later periods, changes in hygiene and sanitation have been much less dramatic, and thus the confounding factors are less around the introduction of measles, rubella and Haemophilus B vaccinations.

Events following reductions in vaccination

In several countries since 1960, reductions in the use of some vaccines were followed by increases in the diseases' morbidity and mortality.

It has been suggested that, because the death and illness rate is so low in most first world countries, there is no need for vaccination. This could be interpreted to mean that when a public health measure is effective, it should be discontinued.

In the absence of assertions that contracting infectious diseases is either a necessary part of development, or confers specific benefits apart from specific (to that disease) immunity, it is commonly accepted that surveillance for infectious disease and isolation of individuals contracting an infectious disease are cornerstones of public health policy. In the 19th century, the city of Leicester in the UK achieved a high level of isolation of smallpox cases and great reduction in spread compared to other areas. The mainstay of Leicester's approach to conquering smallpox was to decline vaccination and put their public funds into sanitary improvements. Bigg's account of the public health procedures in Leicester, presented as evidence to the Royal Commission, refers to erysipelas, an infection of the superficial tissues which was a complication of any surgical procedure.

A component of current-day anti-vaccinationist argument is against the medical establishment . This renders those convinced more likely to avoid reporting illness, and weakens the tracing and control of infection . An imported measles case in Iowa is one illustration of the problem this might cause.

UK: DPT 1970s-80s

In the 1970's and 1980's there was a campaign (in which the newspaper The Sunday Times was particularly involved) against the use of the Diphtheria, Pertussis and Tetanus (DPT) "triple jab" vaccine. This lead to a decline in public confidence and an increase in cases of pertussis (whooping cough) and the subsequent death of some children. The scare ended in the UK after a March 1988 ruling in the High Court in London that, on the balance of

probabilities, the vaccine did not cause permanent neurological damage [3]. A similar pattern was thought to occur in the 1990's with the MMR vaccine causing autism; the single study this was based on has now been discredited.

The Netherlands: measles (1999-2000)

An outbreak at a religious community and school in The Netherlands illustrates the effect of measles in an unvaccinated population.[8] The population in the several provinces affected had a high level of immunisation with the exception of one of the religious denominations who traditionally do not accept vaccination. The three measles-related deaths and 68 hospitalizations that occurred among 2961 cases in the Netherlands demonstrate that measles can be severe and may result in death even in industrialized countries.

Ireland: measles (2000)

From late 1999 until the summer of 2000, there was a measles outbreak in North Dublin, Ireland. At the time, the national immunisation level had fallen below 80%, and in part of north Dublin the level was around 60%. There were more than 100 hospital admissions from over 300 cases. Three children died and several more were gravely ill, some requiring mechanical ventilation to recover.[9],[10]

Anti-vaccinationist material

Anti-vaccination writings on the Internet are characterised by a number of differences from medical and scientific literature.[5] These include:

- Promiscuous copying and reduplication.[11]
- Tendency to be without corrections, even when an initial report is shown to be false (e.g. Donnegan and Schreiber references below). See also absent correction
- Deficiency of references to allow readers, should they wish, to check sources.[12]
- Personal attacks on individual doctors.
- Dishonest or fallacious arguments.[13]
- The sites show a high degree of interlinkage.[11]

There is a considerable overlap with homeopathy and various conspiracy theories, and a subset of the material shades into the appearance of psychosis.[14] An example, which vaccinationists say is dishonest, is the dismissal of immunisation by some critics because it has not eliminated any disease. In 1979 the World Health Organisation (WHO) announced that smallpox had been eradicated; WHO described a huge effort involving many people and various public health strategies, of which immunisation was an important one. Anti-vaccinationists present this as an assertion that the result came solely by vaccination, and then assert that instead it came about solely by historical force.

Over each time period, infectious disease mortality has been falling for all common diseases (UK Office for National Statistics); anti-vaccinationists argue that this is because of improvements in nutrition and living conditions, not because of immunisation.

Anti-vaccination organisations

Historical

Aims and results of the early movements

In Massachusetts, the argument continued from that about variolation, with a minority religious view strongly put that others should eschew immunisation and accept the smallpox that God sent. Cotton Mather and other leaders favoured efforts to prevent disease.

In the USA, the Commonwealth of Massachusetts was the first to make vaccination mandatory, in 1908. In the UK, vaccination was provided free from 1840 under the Vaccination Act. In 1873, a further Vaccination Act made vaccination compulsory. Resistance to compulsion grew, and in 1885, after riots in Leicester, a Royal Commission sat and reported 7 years later, recommending the abolition of cumulative penalties. This was accomplished in the 1898 Act, which also introduced a conscience clause, allowing parents who did not believe that vaccination was efficacious or safe to obtain exemption. This extended the concept of the "conscientious objector" in English law. The aims of the protesters and organisations had thus been achieved in *1898*.

Name	Started	Finished	Location	Unique Proposition / Notes
Anti-vaccination Society	1798		Boston USA	Against the will of God
Anti-Compulsory Vaccination League	1866	1880 (segue)		Mr. R. B. Gibbs (d. 1871) started it . Revived 1876, President: Rev. W. Hume-Rothery
the Anti-Vaccination Society of America	1879			
New England Anti-Compulsory Vaccination League	1882			
Anti-Vaccination League of New York City	1885			
London Society for the Abolition of Compulsory Vaccination	1880	1896 (segue)	Victoria Street, Westminster, London	Secretary: Mr William Young. Adopted The Vaccination Inquirer established 1879 William Tebb as the organ of the Society. Published: • 14 "Vaccination Tracts" 1877 - completed by Dr Garth Wilkinson in 1879 • 1879, "Vaccination Tracts" • 1882 THE FABLE OF THE SMALL-POX HOSPITAL NURSES SAVED • FROM SMALL-POX BY RE-VACCINATION • April 1883 to March 1884, The Vaccination Inquirer Vol V (book) The movement grew and the London Society soon became national so reformed as ...
National Anti-Vaccination League	1896 (Feb)	before 1970?	England	objectives:— repeal of the Vaccination Acts; disestablishment and disendowment of vaccination; abolition of all regulations in regard to vaccination as conditions of employment in State Departments or of admission to Educational or other Institutions. Added in 1921:— vindication of the legitimate freedom of the subject in matters of medical treatment

An organisation with a general anti-vaccination view but other more significant characteristics was the Nazi party.[15]

Current

Name	Started	Finished	Location	Membership	Unique Proposition / Notes
Vaccination Liberation (USA)	Contemporary				Website: www.vaclib.org
VRAN (Canada)					Website: www.vran.org
AVN (Australia)					Website: www.avn.org.au

Since the reversion from compulsory immunisation in the UK, opposition has continued at a lower level. After 1993, several national organisations appeared on the Web. Continuity with the older organisations is not apparent.

Opposition could no longer focus on the right to determine what is done to one's children, and therefore the primary arguments against vaccination changed. Focus transferred to arguments that immunisation did not have an effect; that it had a negative, rather than beneficial effect; or that although immunisation had a beneficial effect in the short term, any benefit may be negated by long term negative consequences.

These changes have resulted in arguments based upon hypotheses that are susceptible to disproof rather than philosophical questions of the relationship of individuals to state or deity.

General

The historian Nadja Durbach [6] notes that in the early 19th century, the anti-vaccination movement drew members from across a wide range of society. Fitzpatrick reviewing it adds that in recent years, it has been reduced to a predominantly middle-class phenomenon.

The state

"Vaccination is unique among de facto mandatory requirements in the modern era, requiring individuals to accept the injection of a medicine or medicinal agent into their bodies, and it has provoked a spirited opposition. This opposition began with the first vaccinations, has not ceased, and probably never will. From this realisation arises a difficult issue: how should the mainstream medical authorities approach the anti-vaccination movement? A passive reaction could be construed as endangering the health of society, whereas a heavy handed approach can threaten the values of individual liberty and freedom of expression that we cherish." BMJ

Most states in the USA require immunization, or obtaining exemption, before enrolment in public school. Exemptions are typically for people who have compromised immune systems, allergies to the components used in vaccinations or strongly-held objections. The American Academy of Pediatrics considers parental waivers of immunization a form of child abuse and neglect.

Anti-vaccinationist organisations publicise the procedure for obtaining exemption. Immunizations are often compulsory for military enlistment.

Anti-vaccinationist assertions

Many assertions are replicated in several websites and repeated by individuals who have been categorised as anti-vaccinationist. Peter Morrell, a part time academic in England, describes one set. They are generally presented as individual propositions, rather than a nesting set of propositions ; this contrasts with scientific argument where classification and consolidation are fundamental

No benefit

Some anti-vaccinationists offering alternative medical practices assert that there has never been any benefit to public health from vaccination[16]. Similarly they assert that all the reduction of communicable diseases which were rampant in conditions where overcrowding, poor sanitation, almost non-existent hygiene and a yearly period of very restricted diet existed, are reduced because of changes in conditions excepting vaccination .

50 percent

As in:

- "50% of deaths occur in vaccinated children" with the implication that there is an even chance regardless of immunisation, and that the immunised population is identical to the unimmunised .
- "50% of deaths occur in children below the age of vaccination" with the implication that they would not be protected by personal immunisation, and therefore not protected at all . Herd immunity is not mentioned.

90 percent

A recurring argument is that a 90% (eg 99.4% for measles in England and Wales from 1901/2 averaged) reduction in a specific disease occurred between two dates, the latter just before introduction of vaccination or immunisation against that disease, and that therefore any subsequent reduction is due to the same forces of history, and none of it is because of vaccination.

(See also **vaccine controversy**)

In on-line responses

Responses to papers or reports of scientific or political enquiry in the BMJ attract responses repeatedly deploying characteristic arguments in characteristic fashion from a small population of frequent responders [10]. Mainstream doctors regard these arguments as having been refuted.

Attacks on a broad front

Science

Assertions that immunisation cannot work because the theory on which it works is incorrect have been made .

Doctors' behaviour

In 2006 immunisation of medical, nursing and paramedical staff in the UK national health service is believed to be complete .

Cell-lines

A reluctance to use (viral) vaccines derived from human cell-lines is a definite principled objection. Secular ethical, humanist and mainstream religious views generally do not reject them. The element of presentation of the argument, in terms of absolutes and the evil of those preparing the vaccines distinguishes arguments from an anti-vaccinationist stance from the discussion of proportionate benefit and harm in a continuum of ethics.

Thiomersal

Thiomersal is being phased out (already in some European countries) and the USA is following. Recently, largely in the USA, it has been suggested that the organic mercury content of thiomersal in child vaccines might contribute to autism.[17][18] The 2004 Institute of Medicine panel favoured rejecting any causal relationship between thiomersal-containing vaccines and autism. The interests in this are vested, for example, governments wishing public health policies to proceed, pharmaceutical companies preferring not to pay huge damages, and (in the absence of no-fault compensation) large monetary gains for successful litigants and their counsel. Anti-vaccination sites publicise the assertions of danger more prominently than these findings , or the fact that thiomersal has recently (eg Oct 2004 in the UK) been removed from many vaccines for use in the Western world (but not the third world).

Effect on public morality

In the USA, some conservative Christian groups, for instance the Family Research Council, have opposed mandatory vaccination for diseases that are typically spread via sexual contact (e.g. Hepatitis and HPV). They believe that the possibility of disease serves as a deterrent against risky sexual contact, and that removing the possibility of disease would have the unintended side effect of encouraging risky sexual contact, particularly among teenagers.[19]

Publications

Historical

- 1884 Compulsory Vaccination in England by William Tebb
1885 The Story of a Great Delusion by William White
1898 Vaccination A Delusion by Alfred Russel Wallace
1936 The Case Against Vaccination by M. Beddow Bayly M.R.C.S., L.R.C.P.
1951 The Truth About Vaccination and Immunization by Lily Loat
1957 The Poisoned Needle by Eleanor McBean

Recent

- 1990 Universal Immunization: Miracle or Masterful Mirage by Dr. Raymond Obomsawin
1993 Vaccination: 100 years of orthodox research shows that vaccines represent an assault on the immune system by Viera Scheibner. ISBN 064615124
2000 Behavioural Problems in Childhood by Viera Scheibner. ISBN 0-9578007-0-3
2004 The Vaccination Nonsense by Dr. med. Gerhard Buchwald ISBN 3-8334-2508-3

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12. ^ Davies P, Chapman S, Leask J (2002). "Antivaccination activists on the world wide web.". Arch Dis Child *87* (1): 22-5. PMID 12089115.

13. ^ **Ed Friedlander.** The Anti-Immunization Activists: A Pattern of Deception**. Retrieved on 2006-11-02.**

14. ^ Schlafly, Roger (2003) Is Vaccination Dissent Dangerous? Journal of American Physicians and Surgeons 8(2):57. Source (pdf)
15. ^ Steve Fuller (20 August 2005). "What if...the Nazis had won" (Abstract). New Scientist (2513).
16. ^ Dr. med. Gerhard Buchwald (Ref: The Vaccination Nonsense. ISBN 3-8334-2508-3 page 108. Asserts that vaccination has never provided any benefit.

17. ^ **"**Autism and Vaccines -- Activists wage a nasty campaign to silence scientists.**",** *Wall Street Journal***, February 16, 2004. Retrieved on 2006-11-02.**

18. ^ "The Truth About Thimerosal -- Democrats and trial lawyers play politics with vaccine liability.", Wall Street Journal, December 5, 2002. Retrieved on 2006-11-02. - WSJ OpEd describing this as anti-vaccinationist activity
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Vaccine controversy

The *vaccine controversy* encompasses many issues over the benefits and risks of vaccines.

Vaccines are widely credited with reducing the prevalence and consequences of many diseases. National and international public health organizations have made vaccination a central part of their strategies. The consensus of health organizations and medical doctors is that mass vaccination campaigns have been an essential and effective component of eradication or control of several deadly diseases via individual and herd immunity.

Critics question the claimed efficacy and safety of such programs, often citing lack of research on the adverse effects as the cause. The medical community, however, overwhelmingly supports vaccination as an effective and safe means of preventing the spread and reducing the impact of infectious illnesses. The majority of public health advocates holds the opinion that the benefit to the public justifies mandatory programs.

Research continues into both the development of new vaccines for a broadening array of diseases and the efficacy and safety of vaccines already in common use.

The case for widespread vaccines

Public health officials, the medical community and public opinion overwhelmingly agree that children should routinely be vaccinated against a range of diseases, such as measles, polio, diphtheria, rubella, tetanus, pertussis, hepatitis B, and others. Some vulnerable groups are also advised to be vaccinated against influenza. Supporters of widespread vaccination policies contend that:

- Vaccines have saved more lives than any other form of medical intervention. Among the most striking successes are the worldwide destruction of smallpox and the near eradication of polio.
- Vaccines are a cost-effective way of ensuring health, compared to treatment of a manifest disease. Routine childhood immunization saves about $40 billion in overall healthcare and social costs per birth year cohort vaccinated.
- Vaccines prevent epidemics in vulnerable areas. When vaccination against polio was recently halted in Nigeria, for instance, the number of cases significantly rose. A recent measles outbreak in 2005 in Indiana was attributed to lack of vaccination among children whose parents refused vaccination
- Critics of vaccination often lack relevant qualifications.
- Other critics of vaccination, such as Robert F. Kennedy, Jr. and Andrew Wakefield, are part of a plaintiffs' lawyers' campaign to generate contingent fees from litigation against vaccine manufacturers using junk science.
- Physicians almost uniformly support polyvalent (more than one antigen) vaccines, such as DPT and MMR, as being in the best interests of the child. The reasons given are that it reduces the unprotected exposure to all but one of the components over that of spaced immunization with single components, one injection is less uncomfortable than several, and it is more cost-effective for parents.
- If individual or multiple vaccinations were to "weaken the immune system", then they would be expected to increase hospitalization for other infections following immunization. Epidemiological surveys give a probability below one in a thousand that this happens. The statistical power of the study — given the Cohort size— is too small to reduce uncertainty further.

Criticism of widespread vaccine policy

The practice of vaccination has been opposed by some since its inception in the late 18th century, but criticism has become more visible in the US and some other developed countries in recent years, roughly paralleling the widespread availability of online information. While positions vary from outright rejection of the practice to calls for more selective and cautious use of vaccination, one or several of the following arguments are typically invoked:

- Critics claim that the public health benefits of vaccinations are exaggerated. They further claim that the mortality rates of some illnesses were already dramatically reduced before vaccines were introduced, and claim that further reductions cannot immediately be attributed to vaccines.
- Secondary and long-term effects on the immune system from introducing immunogens and adjuvants directly into the body are not fully

understood. Some autoimmune diseases like Acute disseminated encephalomyelitis, Guillain-Barré syndrome, Transverse myelitis and multiple sclerosis are known to be connected to vaccines, which suggests other autoimmune disorders might also be vaccine-related [1][2]

- The recommended vaccination schedule does not consider the cumulative effect of being exposed to multiple immunogens at the same time and at a young age.
- At least some vaccine studies did not include such young children (e.g., 5 week old infants, 2 month old infants), yet vaccination schedules start with newborns. There can be a vast difference between the weight and all around development of a newborn baby versus a toddler, yet this is not accounted for.
- Opponents of current vaccination policy question whether vaccinations actually create immunity against the targeted diseases, since some people who have been vaccinated still contracted the illness.
- By not exposing children to common childhood illnesses, they may be more susceptible to diseases at a point when their immune system is weakened, e.g., at an old age or when sick for other reasons.
- As is true with any medication, adverse events to the vaccine (even when rare) may be worse than the disease itself, and there are isolated reports of serious health damage and even death, within hours or a few days of vaccination. Although there are now various national databases where reported reactions can be recorded, anti-vacinationists claim that serious adverse events are grossly under-reported.
- There are a number of possible conflicts of interest that may affect the research design, findings, and opinions about vaccines, including financial interests of companies, the self-regulatory mechanism of medical doctors, and fear of the consequences should vaccines be found to be dangerous (see 2000 Simpsonwood CDC conference for example of such fears). But there are also concerns that opponents of vaccines may be seeking to enrich themselves through litigation or the sale of alternatives, by spreading fear and misjudgment among the public.
- Religious objections, by certain churches and by Christian Scientists to all forms of medical intervention.
- In many studies, adverse effects of vaccines are actively monitored only for a short time, e.g. 14 days.
- In many studies, the vaccine efficacy and safety research is not done by comparing to a group not receiving the vaccine, but to a group receiving a different vaccine for a different disease or a coctail of vaccine additives (e.g. aluminum adjuvants) - thus the research is not designed to show and can not show real vaccine efficacy or safety

The MMR controversy

Controversy has arisen regarding the safety of the MMR vaccine, because a handful of scientists and parents argue that the vaccine is the cause of the increased incidence of autism noted in western countries and Japan, and bowel disorders such as Crohn's disease. A theory advanced by proponents of the link is that the MMR vaccine overwhelms an immune system they assert is already struggling from the effect of thimerosal contained in previous vaccines. They assert that live measles virus in the formulation of the MMR is detrimental to susceptible individuals in a fashion in which wild measles never was.

During the 1980s and 1990s, a number of lawsuits were brought in the United States against manufacturers of vaccines, alleging the vaccines had caused a variety of physical and mental disorders in children. While these were inconclusive, they did lead to a massive jump in the costs of the MMR vaccine, as pharmaceutical companies sought to cover potential liabilities by lobbying for legislative protection. By 1993, Merck KGaA had become the only company willing to sell MMR vaccines in the United States and the United Kingdom. Two other MMR vaccines were withdrawn in the UK in 1992 on safety grounds arising from the strain of mumps component.

In September 1995, the Legal Aid Board in the UK granted a number of families financial assistance to pursue legal claims against the state health authorities and the vaccine's manufacturers, claiming that their children were killed or seriously injured by the MMR vaccine. A pressure group called JABS (Justice, Awareness, Basic Support) was established to represent families with children who, their parents said, were "vaccine-damaged."

In 1996, in New Zealand claims by an academic from Melbourne University that MMR contained a human blood product, serum albumin, and could therefore spread Creutzfeldt-Jakob disease caused anxiety. This did not last, since serum albumin was not an ingredient of the MMR vaccine.

Dr. Andrew Wakefield's report

1998 Lancet paper

In February 1998, a group led by Dr. Andrew Wakefield wrote a paper (on which almost all the other authors later issued a retraction of an interepretation; see below), Ileal-lymphoid-nodular hyperplasia, non-specific colitis, and pervasive developmental disorder in children published in the respected medical journal The Lancet. The report analysed the cases of twelve children with developmental disorders admitted to the Royal Free Hospital in north London in 1996-1997, described a collection of bowel symptoms, which Wakefield asserted was evidence of a possible novel syndrome, which he would later call autistic enterocolitis, and recommended further study into the possible link between the condition and environmental triggers, i.e., the MMR vaccine. The paper proposed links between gastrointestinal symptoms and developmental disorders in twelve children that were alleged to be associated in time with MMR vaccination. No conclusions about causal links, such as that MMR could lead to autism, were reached. However, at a press conference before the paper's publication, Dr Wakefield said that he thought it prudent to use single vaccines instead of the MMR triple vaccine until this could be ruled out as an environmental trigger, given that parents of eight of the twelve children studied were said to have blamed the MMR

vaccine, saying that symptoms of autism had set in within days of vaccination at approximately 14 months. He declared, "I can't support the continued use of these three vaccines given in combination until this issue has been resolved." In a video news release, issued by the hospital to broadcasters in advance of the press conference, he called for MMR to be "suspended in favour of the single vaccines."

Controversy following publication of report

The paper, press conference and video sparked a major health scare in the United Kingdom. The subsequent debate became polarised. Wakefield's research was misused by parties from both sides of the argument. The controversy was seized upon by some UK newspapers, which argued that separate vaccines ought to be available on the National Health Service (NHS) (It can be argued that these newspapers may have been serving their own interest by promoting this "health scare story" up the news agenda). Wakefield became subject to attacks, his critics questioning the validity and the ethics of the research. The UK government and medical authorities, such as the NHS, stressed extensive epidemiological evidence that failed to show any connection between MMR and developmental disorders. These denials were disbelieved by some parents, not least because previous government pronouncements on safety had been faulty, such as in the 'Mad Cow' (BSE) affair. The government was also alleged to be unwilling to support the use of separate vaccines because the NHS could not afford them. As a result, the takeup of MMR dropped sharply, from 92% in 1996 to 84% in 2002. In some parts of London, it was said to be as low as 60% - far below the rate thought to be needed to avoid an epidemic of measles. Although an epidemic has not yet occurred, measles rates have risen and doctors have warned of the likelihood of a future epidemic, because of the failure of the protection offered by herd immunity.

A factor in the controversy is that only the combined vaccine is available through the UK National Health Service; those who do not wish to have it given to their children must either have the separate vaccines given privately, or not vaccinate their children at all. The Prime Minister, Tony Blair, has refused to state whether his son Leo has received the MMR vaccine, but has strongly supported the vaccine in public. The Chancellor, Gordon Brown, has confirmed his son has been immunised[3].

The great majority of doctors prefer to administer the combined vaccine rather than the separate ones, as it is less distressing to the child, and parents are more likely to attend for one vaccination than for three.

Epidemiologic research on hundreds of thousands of children in numerous studies continues to show no link between MMR and autism. Critics of these epidemiology studies, such as retired British clinician John Walker-Smith, although a supporter of the triple vaccine, have pointed out that epidemiology is a 'blunt tool' and may miss causal relationships. For example, it can be difficult to find two populations of sufficient size which differ only in whether they were vaccinated.

Dr. Wakefield left his job at the Royal Free Hospital in 2001. His continued research includes involvement in scientific collaborations in the U.S and Europe, and a report on possible immunologic, metabolic, and pathologic changes occurring in what Wakefield has called "autistic enterocolitis", links between intestinal disease and neurologic disorders in

children, and the potential relationship of these disorders to environmental causes, such as vaccines.

Conflict of interest allegations

In February 2004, it emerged that when Wakefield had published The Lancet report, £55,000 funding was received by the Royal Free Hospital from lawyers seeking evidence of any link between autism and the MMR vaccine. According to a Sunday Times investigation, several of the parents quoted as saying that MMR had damaged their children were also litigants. Although Wakefield maintains the funding was properly disclosed from the outset, allegations have been made that the funding was not revealed to either The Lancet or Wakefield's co-researchers. On February 20, 2005, The Lancet said it should have never published Wakefield's study, which was "flawed" because Dr Wakefield had "a fatal conflict of interest." Several of Dr. Wakefield's co-researchers also strongly criticised the lack of disclosure.

Retraction of an interpretation of the Lancet paper

The investigation which led to 10 of the 13 authors of the 1998 Lancet paper formally retracting the interpretation that the article claimed a link between MMR and autism was carried out by Brian Deer for The Sunday Times of London. Deer continued his investigation in a British television documentary, "MMR: What They Didn't Tell You", broadcast on November 18, 2004. This documentary alleged that Wakefield had applied for patents on a vaccine that was a rival of the MMR vaccine, and that he knew of test results from his own laboratory at the Royal Free hospital that contradicted his claims.

General Medical Council Investigation

The General Medical Council, which is responsible for licensing doctors and Supervising Medical Ethics in the UK were reported to be investigating the affair and in June 2006 was reported to be prepared to accuse Wakefield of four charges: "that he published inadequately founded research, failed to obtain ethical committee approval for the work, obtained funding for it improperly, and subjected children to "unnecessary and invasive investigations." This could result in him being struck off the Medical Register in the UK.

Recent studies

Epidemiological research continues to show a dramatic increase in the incidence of autism, but whether the increase is real, rather than an artifact of changes in diagnosis and reporting, is unknown, and no causal connection has been demonstrated to the MMR vaccine. Since Wakefield's paper, there has been substantial clinical research investigating his claim to have found measles virus located in the gut of proportion of children, much of which has been financed by litigation, with the results not reported on legal grounds.

- In October 2004, the Journal of American Physicians and Surgeons, formerly the Medical Sentinel, magazine of the conservative Association of

American Physicians and Surgeons, published a paper by Wakefield supporters and concluded that "Developing safer vaccination strategies and supporting further investigation of the hypothesized link between the MMR vaccine and autism should have a high priority." It also noted that in Denmark Thimerosal is eliminated as a factor in any relationship between MMR and autism.

- Also in October 2004, a review, financed by the European Union, was published in the October 2004 edition of Vaccine[4] that assessed the evidence given in 120 other studies and considered unintended effects of the MMR vaccine. The authors concluded that
    - the vaccine is associated with some positive and negative side effects,
    - it was "unlikely" that there was a connection between MMR and autism, and
    - "The design and reporting of safety outcomes in MMR vaccine studies ... are largely inadequate".
- In January 2005, intensive research in a single county in Minnesota reported an eightfold increase in the incidence of autism over a period beginning in the early eighties and ending in the late nineties but found no evidence of a link with MMR. The authors of the research suggested that the increase in autism was due to an increased awareness of the disorder, a growth in services, and changing definitions.
- Japan provided a natural experiment on the subject: combined MMR vaccine was introduced in 1989, but the programme was terminated in 1993 and only single vaccines used thereafter.[21] In March 2005 a study of over 30,000 children (278 cases) born in one district of Yokohama concluded "The incidence of all autistic spectrum disorders (ASD), and of autism, continued to rise after MMR vaccine was discontinued. The incidence of autism was higher in children born after 1992 who were not vaccinated with MMR than in children born before 1992 who were vaccinated. The incidence of autism associated with regression was the same during the use of MMR and after it was discontinued." Autism rose (from 46-86 cases per 10,000 children, to 97-161/10,000). The authors concluded: "The significance of this finding is that MMR vaccination is most unlikely to be a main cause of ASD, that it cannot explain the rise over time in the incidence of ASD, and that withdrawal of MMR in countries where it is still being used cannot be expected to lead to a reduction in the incidence of ASD."[5] This study did not question whether or not both MMR and separate vaccines were capable of contributing to ASD, Crohns and other disorders; with separate vaccines, rather than MMR, being responsible for a more severe effect.
- Dr. Wakefield contends the pattern of autism rates revealed by the data support his hypothesis . His views, however, have found little support.[6]
- In October 2005, the Cochrane Library published a review of 31 scientific studies, and concluded that "there was no credible evidence behind claims of harm from the MMR vaccination" and "MMR is an important vaccine that has prevented diseases that still carry a heavy burden of death ....."[23] However the authors of the report also stated that "the design and reporting of

safety outcomes in MMR vaccine studies, both pre- and post-marketing, are largely inadequate."[7] Cochrane, based in Oxford, England, is widely regarded by scientists as the most authoritative independent reviewer of medical literature, and the custodian of evidence-based medicine.

- A Journalist for UPI, Dan Olmsted, has conducted a journalistic investigation reported in his "Age of Autism" column and did not find many never-vaccinated children with autism. Olmsted looked for autistic children among unvaccinated Amish; in a subset of homeschooled children who are not vaccinated for religious reasons; and in a pediatric practice in Chicago with several thousand never-vaccinated children. Partly as a result of this, a U.S. Congresswoman has produced a draft Autism Bill
- In 2006 a study is underway, led by Arthur Krigsman of New York University School of Medicine, involving 275 children. Serious intestinal inflammations have been found in some of the autistic children and biopsies of gut tissue have been performed on 82 of them. Of these, 70 are said to have shown evidence of the measles virus. The study is yet to be completed or peer reviewed.[8]

Vaccination supporters

Supporters of vaccination, which includes most medical organizations:

- Bono

Rosalynn Carter
Eric Fombonne, MD, FRCP,
Thomas Francis, Jr., MD
Robert Koch, MD
Edward Jenner, MD
Paul Offit, MD
William Osler, MD "the father of modern medicine"
Louis Pasteur
Albert Sabin
Jonas Salk, MD
Thomas Verstraeten, MD, MSc
Almroth Wright

Organizations

- Bill & Melinda Gates Foundation

Center for Disease Control
European Medicines Agency
International Red Cross and Red Crescent Movement
Health Canada

Lægemiddelstyrelsen
Médecins Sans Frontières
Medicines and Healthcare products Regulatory Agency
Norwegian Medicines Agency
Royal Swedish Academy of Sciences, administrators of the Nobel Prize for Medicine
Secretaria de Salud
World Health Organization

Vaccination critics

- Maurice Beddow Bayly, MRCS, LRCP

Sallie Bernard
Liz Birt
Mark Blaxill, MBA
Jeff Bradstreet, MD
Patty Brennan
Gerhard Buchwald, MD
Rep. Dan Burton (R-Indiana)
Jonathan Campbell
Alan Cantwell, MD
James Compton-Burnett, MD
Harris Coulter, PhD
Charles Creighton, MD, MA, MB, CM
Judith A. DeCava, BS, CNC
Richard Deth, PhD
Barbara Loe Fisher, DC
Mark Geier, MD, PhD
Walter Hadwen, MD, MRCS, MRCP
Sen. Chuck Hagel (R-Nebraska)
Boyd Haley, PhD
Sepp Hasslberger
Archie Kalokerinos, AMM, MBBS, PhD, FAPM
Robert F. Kennedy, Jr.
David Kirby
Arthur Krigsman, MD
Lily Loat
Bill Maher
Robert Mendelsohn, MD
Joseph Mercola, DO
Neil Z. Miller, BA
Jamie Murphy
Randall Neustaedter, OMD
Gary Null
Dan Olmsted

Charles Pearce, MD
Bernard Rimland, PhD
Lyn Redwood, RN, MSN,
Rick Rollens
Diane Rozario
Viera Scheibner, PhD
William Tebb
Vijendra K. Singh, PhD
Andrew Wakefield, MD
Lord Alfred Wallace
Rep. Dave Weldon, MD (R-Florida)
Edward Yazbak, MD, FAAP

Organizations

- A-CHAMP

Generation Rescue
Health Advocacy in the Public Interest
Homefirst Health Services
National Anti-Vaccination League (long defunct)
National Vaccine Information Center
Safe Minds
Thoughtful House

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Antisense therapy

Antisense therapy is a form of treatment for genetic disorders or infections. When the genetic sequence of a particular gene is known to be causative of a particular disease, it is possible to synthesize a strand of nucleic acid (DNA, RNA or a chemical analogue) that will bind to the messenger RNA (mRNA) produced by that gene and inactivate it, effectively turning that gene "off".

This synthesized nucleic acid is termed an "anti-sense" oligonucleotide because its base sequence is complementary to the gene's messenger RNA (mRNA), which is called the "sense" sequence (so that a sense segment of mRNA " 5'-AAGGUC-3' " would be blocked by the anti-sense mRNA segment " 3'-UUCCAG-5' ").

Antisense drugs are being researched to treat lung cancer, diabetes and diseases such as asthma and arthritis with an inflammatory component. Most potential therapies have not yet produced significant clinical results, though one antisense drug, fomivirsen (marketed as Vitravene), has been approved by the US Food and Drug Administration (FDA) as a treatment for cytomegalovirus retinitis.

See also

- antisense

Biochemical engineering

Biochemical engineering is a branch of chemical engineering that mainly deals with the design and construction of unit processes that involve biological organisms or molecules. Biochemical engineering is often taught as a supplementary option to chemical engineering due to the similarities in both the background subject curriculum and problem-solving techniques used by both professions. Its applications are used in the pharmaceutical, biotechnology, and water treatment industries.

The Bioreactor

A *bioreactor* may refer to any device or system that supports a biologically active environment. In one case, a bioreactor is a vessel in which is carried out a chemical process which involves organisms or biochemically active substances derived from such organisms. This process can either be aerobic or anaerobic. These bioreactors are commonly cylindrical, ranging in size from some liter to cube meters, and are often made of stainless steel.

A bioreactor may also refer to a device or system meant to grow cells or tissues in the context of cell culture. These devices are being developed for use in tissue engineering.

On the basis of *mode of operation*, a bioreactor may be classified as batch, fed batch or continuous (e.g. Continuous stirred-tank reactor model). An example of a bioreactor is the chemostat.

Organism growing in bioreactor may be suspended or immobilized . The simplest, where cells are immobilized, is a Petri dish with agar gel. Large scale immobilized cell bioreactors are:

- packed bed
- fibrous bed
- membrane

Bioreactor design

Bioreactor design is quite a complex engineering task. Under optimum conditions the microorganisms or cells are able to perform their desired function with great efficiency. The bioreactor's environmental conditions like gas (i.e., air, oxygen, nitrogen, carbon dioxide) flowrates, temperature, pH and dissolved oxygen levels, and agitation speed/circulation rate need to be closely monitored and controlled.

Most industrial bioreactor manufacturers use vessels, sensors, controllers, and a control system, networked together for their bioreactor system, see programmable logic controller (PLC).

Fouling can harm the overall sterility and efficiency of the bioreactor, especially the heat exchangers. To avoid it the bioreactor must be easily cleanable and must be as smooth as possible (therefore the round shape).

A heat exchanger is needed to maintain the bioprocess at a constant temperature. Biological fermentation is a major source of heat, therefore in most cases bioreactors need water refrigeration. They can be refrigerated with an external jacket or, for very large vessels, with internal coils.

In an aerobic process, optimal oxygen transfer is perhaps the most difficult task to accomplish. Oxygen is poorly soluble in water -and even less in fermentation broths- and is relatively scarce in air (20.8%). Oxygen transfer is usually helped by agitation, that is also needed to mix nutrients and to keep the fermentation homogeneous. There are however limits to the speed of agitation, due both to high power consumption (which is proportional to the cube of the speed of the electric motor) and the damage to organisms due to excessive tip speed.

Industrial bioreactors usually employ bacteria or other simple organisms that can withstand the forces of agitation. They are also simple to sustain, requiring only simple nutrient solutions and can grow at astounding rates.

In bioreactors where the goal is grow cells or tissues for experimental or therapeutic purposes, the design is significantly different from industrial bioreactors. Many cells and tissues, especially mammalian, must have a surface or other structural support in order to grow, and agitated environments are often destructive to these cell types and tissues. Higher organisms also need more complex growth medium.

NASA Tissue Cloning Bioreactor

NASA has developed a new type of bioreactor that artificially grows tissue in cell cultures. NASA's tissue bioreactor can grow heart tissue, skeletal tissue, ligaments, cancer tissue for study, and other types of tissue.

For more information on artificial tissue culture.

Biopharmaceuticals

Biopharmaceuticals are medical drugs (see pharmacology) produced using biotechnology. They are proteins (including antibodies), nucleic acids (DNA, RNA or antisense oligonucleotides) used for therapeutic or in vivo diagnostic purposes, and are produced by means other than direct extraction from a native (non-engineered) biological source. [1]

The first such substance approved for therapeutic use was recombinant human insulin (rHI, trade name Humulin), which was developed by Genentech and marketed by Eli Lilly and Company in 1982.

The large majority of biopharmaceutical products are pharmaceuticals that are derived from life forms. Small molecule drugs are not typically regarded as biopharmaceutical in nature by the industry. However members of the press and the business and financial community often extend the definition to include pharmaceuticals not created through biotechnology. That is, the term has become an oft-used buzzword for a variety of different companies producing new, apparently high-tech pharmaceutical products.

When a biopharmaceutical is developed, the company will typically apply for a patent, which is a grant for exclusive manufacturing rights. This is the primary means by which the developer of the drug can recover the investment cost for development of the biopharmaceutical. The patent laws in the United States and Europe differ somewhat on the requirements for a patent, with the European requirements are perceived as more difficult to satisfy. The total number of patents granted for biopharmaceuticals has risen significantly since the 1970s. In 1978 the total patents granted was 30. This had climbed to 15,600 in 1995, and by 2001 there were 34,527 patent applications.[2]

Within the United States, the Food and Drug Administration (FDA) exerts strict control over the commercial distribution of a pharmaceutical product, including biopharmaceuticals. Approval can require several years of clinical trials, including trials with

human volunteers. Even after the drug is released, it will still be monitored for performance and safety risks.

The manufacture of the drug must satisfy the "current Good Manufacturing Practices" regulations of the FDA. They are typically manufactured in a clean room environment with set standards for the amount of airborne particles.

Classification of biopharmaceuticals

- Blood factors (Factor VIII and Factor IX)
- Thrombolytic agents (tissue plasminogen activator)
- Hormones (Insulin, growth hormone, gonadotrophins)
- Haematopoietic growth factors (Erythropoietin, colony stimulating factors)
- Interferons (Interferons-±, -^{2}, -^{3})
- Interleukin-based products (Interleukin-2)
- Vaccines (Hepatitis B surface antigen)

- Monoclonal antibodies **(Various)**

- Additional products (tumour necrosis factor, therapeutic enzymes)

Uses

- Erythropoietin - Treatment of anaemia
- Interferon-± - Treatment of leukaemia

Interferon-^{2} - Treatment of multiple sclerosis
Monoclonal antibody - Treatment of rheumatoid arthritis
Colony stimulating factors - Treatment of neutropenia
Glucocerebrosidase - Treatment of Gaucher's disease

Large scale production

Biopharmaceuticals may be produced from microbial cells (e.g. recombinant E. coli), mammalian cell lines (see cell culture) and plant cell cultures (see plant tissue culture) in bioreactors of various configurations.

Important issues of concern are cost of production (a low volume, high purity product is desirable) and microbial contamination (by bacteria, viruses, mycoplasma, etc). Alternative platforms of production which are being tested include whole plants (plant-made pharmaceuticals).

Transgenics

A potentially controversial method of producing biopharmaceuticals involves transgenic organisms, particularly plants and animals that have been genetically modified to produce

drugs. The production of these organisms represents a significant risk on the part of the investor, both in terms of the risk of failure to produce the required organism, and in the risk of non-acceptance by government bodies due to the perceived risks and from ethical issues. Biopharmaceutical crops also represent a risk of cross-contamination with non-engineered crops, or crops engineered for non-medical purposes.

One potential approach to this technology is the creation of a transgenic mammal that can produce the biopharmaceutical in its milk (or blood or urine). Once an animal is produced, typically using the pronuclear microinjection method, it becomes efficacious to use cloning technology to create additional offspring that carry the favorable modified genome. [3] The first such drug manufactured from the milk of a genetically-modified goat was ATryn®, but marketing permission was blocked by the European Medicines Agency in February 2006.[4] This decision was reversed in June 2006 and approval was given August 2006. [5]

See also

- Genetic engineering

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Gene therapy

Gene therapy is the insertion of genes into an individual's cells and tissues to treat a disease, and hereditary diseases in particular. Gene therapy typically aims to supplement a defective mutant allele with a functional one. Although the technology is still in its infancy, it has been used with some success. Antisense therapy is not strictly a form of gene therapy, but is often lumped together with them.

Background

In the 1980s, advances in molecular biology had already enabled human genes to be sequenced and cloned. Scientists looking for a method of easily producing proteins — such as insulin, the protein deficient in diabetes mellitus type 1 — investigated introducing human genes to bacterial DNA. The modified bacteria then produce the corresponding protein, which can be harvested and injected in people who cannot produce it naturally.

On September 14, 1990 researchers at the U.S. National Institutes of Health performed the first approved gene therapy procedure on four-year old Ashanti DeSilva. Born with a rare genetic disease called severe combined immunodeficiency (SCID), she lacked a healthy immune system, and was vulnerable to every passing germ. Children with this illness usually develop overwhelming infections and rarely survive to adulthood; a common childhood illness like chickenpox is life-threatening. Ashanti led a cloistered existence--avoiding contact with people outside her family, remaining in the sterile environment of her home, and battling frequent illnesses with massive amounts of antibiotics.

In Ashanti's gene therapy procedure, doctors removed white blood cells from the child's body, let the cells grow in the lab, inserted the missing gene into the cells, and then infused the genetically modified blood cells back into the patient's bloodstream. Laboratory tests have shown that the therapy strengthened Ashanti's immune system; she no longer has recurrent colds, she has been allowed to attend school, and she was immunized against whooping cough. This procedure was not a cure; the white blood cells treated genetically only work for a few months, and the process must be repeated every few months. (VII, Thompson [First] 1993).

Although this simplified explanation of a gene therapy procedure sounds like a happy ending, it is little more than an optimistic first chapter in a long story; the road to the first approved gene therapy procedure was rocky and fraught with controversy. The biology of human gene therapy is very complex, and there are many techniques that still need to be developed and diseases that need to be understood more fully before gene therapy can be used appropriately. The public policy debate surrounding the possible use of genetically engineered material in human subjects has been equally complex. Major participants in the debate have come from the fields of biology, government, law, medicine, philosophy, politics, and religion, each bringing different views to the discussion.

Scientists took the logical step of trying to introduce genes straight into human cells, focusing on diseases caused by single-gene defects, such as cystic fibrosis, hemophilia, muscular dystrophy and sickle cell anemia. However, this has been much harder than modifying simple bacteria, primarily because of the problems involved in carrying large sections of DNA and delivering it to the right site on the genome.

Basic process

In most gene therapy studies, a "normal" gene is inserted into the genome to replace an "abnormal," disease-causing gene. A carrier molecule called a vector must be used to deliver the therapeutic gene to the patient's target cells. Currently, the most common vector is a virus that has been genetically altered to carry normal human DNA. Viruses have evolved a

way of encapsulating and delivering their genes to human cells in a pathogenic manner. Scientists have tried to take advantage of this capability and manipulate the virus genome to remove disease-causing genes and insert therapeutic genes.

Target cells such as the patient's liver or lung cells are infected with the vector. The vector then unloads its genetic material containing the therapeutic human gene into the target cell. The generation of a functional protein product from the therapeutic gene restores the target cell to a normal state.

Types of gene therapy

In theory it is possible to transform either somatic cells (most cells of the body) or cells of the germline (such as sperm cells, ova, and their stem cell precursors). All gene therapy so far in people has been directed at somatic cells, whereas germline engineering in humans remains only a highly controversial prospect. For the introduced gene to be transmitted normally to offspring, it needs not only to be inserted into the cell, but also to be incorporated into the chromosomes by genetic recombination.

Somatic gene therapy can be broadly split in to two categories: ex vivo (where cells are modified outside the body and then transplanted back in again) and in vivo (where genes are changed in cells still in the body.) Recombination-based approaches in vivo are especially uncommon, because for most DNA constructs recombination has a very low probability.

Broad methods

There are a variety of different methods to replace or repair the genes targeted in gene therapy.

- A normal gene may be inserted into a nonspecific location within the genome to replace a nonfunctional gene. This approach is most common.
- An abnormal gene could be swapped for a normal gene through homologous recombination.
- The abnormal gene could be repaired through selective reverse mutation, which returns the gene to its normal function.
- The regulation (the degree to which a gene is turned on or off) of a particular gene could be altered.

Vectors in gene therapy

Viruses

All viruses attack their hosts and introduce their genetic material into the host cell as part of their replication cycle. This genetic material contains basic 'instructions' of how to produce more copies of these viruses, hijacking the body's normal production machinery to serve the needs of the virus. The host cell will carry out these instructions and produce additional copies of the virus, leading to more and more cells becoming infected. Some types of viruses actually physically insert their genes into the host's genome (it is the defining

feature of retroviruses, the family of viruses that includes HIV, the virus that causes AIDS). This incorporates the genes of that virus among the genes of the host cell for the life span of that cell.

Doctors and molecular biologists realized that viruses like this could be used as vehicles to carry 'good' genes into a human cell. First, a scientist would remove the genes in the virus that cause disease. Then they would replace those genes with genes encoding the desired effect (for instance, insulin production in the case of diabetics). This procedure must be done in such a way that the genes which allow the virus to insert its genome into its host's genome are left intact. This can be confusing, and requires significant research and understanding of the virus' genes in order to know the function of each. An example:

> A virus is found which replicates by inserting its genes into the host cell's genome. This virus has two genes- A and B. Gene A encodes a protein which allows this virus to insert itself into the host's genome. Gene B actually causes the disease this virus is associated with. Gene C is the "normal" or "desirable" gene we want in the place of gene B. Thus, by re-engineering the virus so that gene B is replaced by gene C, while allowing gene A to properly function, this virus could introduce your 'good gene'- gene C into the host cell's genome without causing any disease.

All this is clearly an oversimplification, and numerous problems exist that prevent gene therapy using viral vectors, such as: trouble preventing undesired effects, ensuring the virus will infect the correct target cell in the body, and ensuring that the inserted gene doesn't disrupt any vital genes already in the genome. However, this basic mode of gene introduction currently shows much promise and doctors and scientists are working hard to fix any potential problems that could exist.

Retroviruses

The genetic material in retroviruses is in the form of RNA molecules, while the genetic material of their hosts is in the form of DNA. When a retrovirus infects a host cell, it will introduce its RNA together with some enzymes into the cell. This RNA molecule from the retrovirus must produce a DNA copy from its RNA molecule before it can be considered for part of the genetic material of the host cell. The process of producing a DNA copy from an RNA molecule is termed reverse transcription. It is carried out by one of the enzymes carried in the virus, called reverse transcriptase. After this DNA copy is produced and is free in the nucleus of the host cell, it must be incorporated into the genome of the host cell. That is, it must be inserted into the large DNA molecules in the cell (the chromosomes). This process is done by another enzyme carried in the virus called integrase.

Now that the genetic material of the virus is incorporated and has become part of the genetic material of the host cell, we can say that the host cell is now modified to contain a new gene. If this host cell divides later, its descendants will all contain the new genes.

One of the problems of gene therapy using retroviruses is that the integrase enzyme can insert the genetic material of the virus in any arbitrary position in the genome of the host. If genetic material happens to be inserted in the middle of one of the original genes of the host cell, this gene will be disrupted (insertional mutagenesis). If the gene happens to be one regulating cell division, uncontrolled cell division (i.e., cancer) can occur. This problem has recently begun to be addressed by utilizing zinc finger nucleases[1] or by including certain

sequences such as the beta-globin locus control region[6] to direct the site of integration to specific chromosomal sites.

Gene therapy trials to treat severe combined immunodeficiency (SCID) were halted or restricted in the USA when leukemia was reported in three of eleven patients treated in the French Therapy X-linked SCID (XSCID) gene therapy trial. Ten XSCID patients treated in England have not presented leukemia to date and have had similar success in immune reconstitution. Gene therapy trials to treat SCID due to deficiency of the Adenosine Deaminase (ADA) enzyme continue with relative success in the USA, Italy and Japan.

Adenoviruses

Adenoviruses are viruses that carry their genetic material in the form of double-stranded DNA. They cause respiratory (especially the common cold), intestinal, and eye infections in humans. When these viruses infect a host cell, they introduce their DNA molecule into the host. The genetic material of the adenoviruses is not incorporated into the host cell's genetic material. The DNA molecule is left free in the nucleus of the host cell, and the instructions in this extra DNA molecule are transcribed just like any other gene. The only difference is that these extra genes are not replicated when the cell is about to undergo cell division so the descendants of that cell will not have the extra gene. As a result, treatment with the adenovirus will require readministration in a growing cell population although the absence of integration into the host cell's genome should prevent the type of cancer seen in the SCID trials. This vector system has shown real promise in treating cancer and indeed the first gene therapy product to be licenced is an adenovirus to treat cancer.

Adeno-associated viruses

Adeno-associated viruses, from the parvovirus family, are small viruses with a genome of single stranded DNA. These viruses can insert genetic material at a specific site on chromosome 19. There are a few disadvantages to using AAV, including the small amount of DNA it can carry (low capacity) and the difficulty in producing it. This type of virus is being used, however, because it is non-pathogenic (most people carry this harmless virus). In contrast to adenoviruses, most people treated with AAV will not build an immune response to remove the virus and the cells that have been successfully treated with it. Several trials with AAV are on-going or in preparation, mainly trying to treat muscle and eye diseases; the two tissues where the virus seems particularly useful. However, clinical trials have also been initiated where AAV vectors are used to deliver genes to the brain. This is possible because AAV viruses can infect non-dividing (quiescent) cells, such as neurons in which their genomes be expressed for a long time. In recent human trials, CD8+ immune cells have recognised the AAV infected cells as compromised and killed these cells accordingly. This action appears to be triggered by part of the capsid or outer coat of the type 2 virus. Recent studies have shown that humans will likely react in the same way against the new serotype 8 AAV as well.

Envelope protein pseudotyping of viral vectors

The viral vectors described above have natural host cell populations that they infect most efficiently. Retroviruses have limited natural host cell ranges, and although adenovirus and adeno-associated virus are able to infect a relatively broader range of cells efficiently, some cell types are refractory to infection by these viruses as well. Attachment to and entry into a susceptible cell is mediated by the protein envelope on the surface of a virus. Retroviruses and adeno-associated viruses have a single protein coating their membrane, while adenoviruses are coated with both an envelope protein and fibers that extend away from the surface of the virus. The envelope proteins on each of these viruses bind to cell-surface molecules such as heparin sulfate, which localizes them upon the surface of the potential host, as well as with the specific protein receptor that either induces entry-promoting structural changes in the viral protein, or localizes the virus in endosomes wherein acidification of the lumen induces this refolding of the viral coat. In either case, entry into potential host cells requires a favorable interaction between a protein on the surface of the virus and a protein on the surface of the cell. For the purposes of gene therapy, one might either want to limit or expand the range of cells susceptible to transduction by a gene therapy vector. To this end, many vectors have been developed in which the endogenous viral envelope proteins have been replaced by either envelope proteins from other viruses, or by chimeric proteins. Such chimera would consist of those parts of the viral protein necessary for incorporation into the virion as well as sequences meant to interact with specific host cell proteins. Viruses in which the envelope proteins have been replaced as described are referred to as pseudotyped viruses. For example, the most popular retroviral vector for use in gene therapy trials has been the lentivirus Simian Immunodeficiency virus coated with the envelope proteins, G-protein, from Vesicular Stomatitus virus. This vector is referred to as VSV G-pseudotyped lentivirus, and infects an almost universal set of cells. This tropism is characteristic of the VSV G-protein with which this vector is coated. Many attempts have been made to limit the tropism of viral vectors to one or a few host cell populations. This advance would allow for the systemic administration of a relatively small amount of vector. The potential for off-target cell modification would be limited, as well as many concerns from the medical community. Most attempts to limit tropism have used chimeric envelope proteins bearing antibody fragments. These vectors show great promise for the development of "magic bullet" gene therapies.

Non-viral methods

Non-viral methods present certain advantages over viral methods; simple large scale production and low host immunogenicity being just two. Previously, low levels of transfection and expression of the gene held non-viral methods at a disadvantage, however recent advances in vector technology has yielded molecules and techniques with transfection efficiencies similar to that of viruses.

Naked DNA

This is the simplest method of non-viral transfection. Clinical trials have been carried out of intramuscular injection of a naked DNA plasmid have occurred with some success, however the expression has been very low in comparison to other methods of transfection. In addition to trials with plasmids, there have been trials with naked PCR product, which have had similar or greater success, however this success does not compare to that of the other methods, leading to research into more efficient methods for delivery of the naked DNA such as electroporation and the use of a "gene gun", which shoots DNA coated gold particles into the cell using high pressure gas.

Oligodeoxynucleotides

The use of synthetic oligodeoxynucleotides in gene therapy is to inactivate the genes involved in the disease process. There are several methods by which this is achieved. One strategy uses antisense specific to the target gene to disrupt the transcription of the faulty gene. Another uses small catalytic molecules of RNA called siRNA to cleave specific unique sequences in the mRNA transcript of the faulty gene, disrupting translation of the faulty mRNA, and therefore expression of the gene. A further strategy uses double stranded oligodeoxynucleotides as a decoy for the transcription factors that are required to activate the transcription of the target gene. The transcription factors bind to the decoys instead of the promoter of the faulty gene which reduces the transcription of the target gene, lowering expression.

Lipoplexes and polyplexes

To improve the delivery of the new DNA into the cell, the DNA must be protected from damage and its entry into the cell must be facilitated. To this end new molecules, lipoplexes and polyplexes, have been created that have the ability to protect the DNA from undesirable degradation during the transfection process.

Plasmid DNA can be covered with lipids in an organized structure like a micelle or a liposome. When the organized structure is complexed with DNA it is called a lipoplex. There are three types of lipoplexes, anionic (negatively charged), neutral or cationic (positively charged). Initially, anionic and neutral lipids were used for the construction of lipoplexes for synthetic vectors. However, although there is little toxicity associated with them, they are compatible with body fluids and there was a possibility of adapting them to be tissue specific, they are complicated and time consuming to produce so attention was turned to the cationic versions.

Cationic lipids, due to their positive charge, naturally complex with the negatively charged DNA. Also as a result of their charge they interact with the cell membrane, endocytosis of the lipoplex occurs and the DNA is released into the cytoplasm. The cationic lipids also protect against degradation of the DNA by the cell.

The most common use of lipoplexes has been in gene transfer into cancer cells, where the supplied genes have activated tumor suppressor control genes in the cell and decrease the activity of oncogenes. Recent studies have shown lipoplexes to be useful in transfecting

respiratory epithelial cells, so they may be used for treatment of genetic respiratory diseases such as cystic fibrosis.

Complexes of polymers with DNA are called polyplexes. Most polyplexes consist of cationic polymers and their production is regulated by ionic interactions. One large difference between the methods of action of polyplexes and lipoplxes is that polyplexes cannot release their DNA load into the cytoplasm, so to this end, co-transfection with endosome-lytic agents (to lyse the endosome that is made during endocytosis, the process by which the polyplex enters the cell) such as inactivated adenovirus must occur. However this isn't always the case, polymers such as polyethylenimine have their own method of endosome disruption.

Hybrid methods

Due to every method of gene transfer having shortcomings, there has been some hybrid methods developed that combine two or more techniques. Virosomes are one example; they combine liposomes with an inactivated HIV or influenza virus. This has been shown to have more efficient gene transfer in respiratory epithelial cells than either viral or liposomal methods alone. Other methods involve mixing other viral vectors with cationic lipids or hybridising viruses.

Recent developments in gene therapy

Scientist at the National Institutes of Health (Bethesda, MD) have successfully treated metastatic melanoma in two patients using killer T cells genetically retargeted to attack the cancer cells. This study constitutes the first demonstration that gene therapy can be effective in treating cancer. The study results have been published in Science (October 2006).

In May 2006 a team of scientists led by Drs. Luigi Naldini and Brian Brown from the San Raffaele Telethon Institute for Gene Therapy (HSR-TIGET) in Milan, Italy reported a breakthrough for gene therapy in which they developed a way to prevent the immune system from rejecting a newly delivered gene. Similar to organ transplanation, gene therapy has been plagued by the problem of immune rejection. So far, delivery of the 'good' gene has been difficult because the immune sytem does not recognize the new gene and rejects the cells carrying it. To overcome this problem, the HSR-TIGET group utilized a newly uncovered network of genes regulated by molecules known as microRNAs. Dr. Naldini's group reasoned that they could use this natural function of microRNA to selectively turn off the identity of their therapeutic gene in cells of the immune system and prevent the gene from being found and destroyed. The researchers injected mice with the gene containing an immune-cell microRNA target sequence, and spectacularly, the mice did not reject the gene, as previously occurred when vectors without the microRNA target sequence were used. This work will have important implications for the treatment of hemophilia and other genetic diseases by gene therapy [1].

In March 2006 an international group of scientists announced the successful use of gene therapy to treat two adult patients for a disease affecting myeloid cells. The study, published

in Nature Medicine, is believed to be the first to show that gene therapy can cure diseases of the myeloid system

University of California, Los Angeles, research team gets genes into the brain using liposomes coated in a polymer called polyethylene glycol (PEG). The transfer of genes into the brain is a significant achievement because viral vectors are too big to get across the "blood-brain barrier." This method has potential for treating Parkinson's disease. See *Undercover genes slip into the brain* at NewScientist.com (March 20, 2003).

RNA interference or gene silencing may be a new way to treat Huntington's. Short pieces of double-stranded RNA (short, interfering RNAs or siRNAs) are used by cells to degrade RNA of a particular sequence. If a siRNA is designed to match the RNA copied from a faulty gene, then the abnormal protein product of that gene will not be produced. See *Gene therapy may switch off Huntington's* at NewScientist.com (March 13, 2003).

New gene therapy approach repairs errors in messenger RNA derived from defective genes. Technique has potential to treat the blood disorder thalassaemia, cystic fibrosis, and some cancers. See *Subtle gene therapy tackles blood disorder* at NewScientist.com (October 11, 2002).

Researchers at Case Western Reserve University and Copernicus Therapeutics are able to create tiny liposomes 25 nanometers across that can carry therapeutic DNA through pores in the nuclear membrane. See *DNA nanoballs boost gene therapy* at NewScientist.com (May 12, 2002).

Sickle cell is successfully treated in mice. See *Murine Gene Therapy Corrects Symptoms of Sickle Cell Disease* from March 18, 2002, issue of The Scientist.

The success of a multi-center trial for treating children with SCID (severe combined immune deficiency or "bubble boy" disease) held from 2000 and 2002 was questioned when two of the ten children treated at the trial's Paris center developed a leukemia-like condition. Clinical trials were halted temporarily in 2002, but resumed after regulatory review of the protocol in the United States, the United Kingdom, France, Italy, and Germany. (V. Cavazzana-Calvo, Thrasher and Mavilio 2004; see also '*Miracle' gene therapy trial halted* at NewScientist.com, October 3, 2002).

Problems and ethics

For the safety of gene therapy, the Weismann barrier is fundamental in the current thinking. Soma-to-germline feedback should therefore be impossible. However, there are indications that the Weissman barrier can be breached. One way it might possibly be breached is if the treatment were somehow misapplied and spread to the testes and therefore would infect the germline against the intentions of the therapy.

Some of the problems of gene therapy include:

- Short-lived nature of gene therapy - Before gene therapy can become a permanent cure for any condition, the therapeutic DNA introduced into target cells must remain functional and the cells containing the therapeutic DNA must be long-lived and stable. Problems with integrating therapeutic DNA into the genome and the rapidly dividing nature of many cells prevent gene therapy from achieving any long-term benefits. Patients will have to undergo multiple rounds of gene therapy.

- Immune response - Anytime a foreign object is introduced into human tissues, the immune system is designed to attack the invader. The risk of stimulating the immune system in a way that reduces gene therapy effectiveness is always a potential risk. Furthermore, the immune system's enhanced response to invaders it has seen before makes it difficult for gene therapy to be repeated in patients.
- Problems with viral vectors - Viruses, while the carrier of choice in most gene therapy studies, present a variety of potential problems to the patient -- toxicity, immune and inflammatory responses, and gene control and targeting issues. In addition, there is always the fear that the viral vector, once inside the patient, may recover its ability to cause disease.
- Multigene disorders - Conditions or disorders that arise from mutations in a single gene are the best candidates for gene therapy. Unfortunately, some of the most commonly occurring disorders, such as heart disease, high blood pressure, Alzheimer's disease, arthritis, and diabetes, are caused by the combined effects of variations in many genes. Multigene or multifactorial disorders such as these would be especially difficult to treat effectively using gene therapy.
- Chance of inducing a tumor - If the DNA is integrated in the wrong place in the genome, for example in a tumor suppressor gene, it could induce a tumor.

In popular culture

Gene therapy plays a major role in the sci-fi series Stargate Atlantis, as a certain type of alien technology can only be used if one has a certain gene which is given to the members of the team through gene therapy. Gene therapy also plays a major role in the plot of the James Bond movie Die Another Day. The Yellow Bastard from Frank Miller's Sin City was also apparently the recipient of gene therapy.

Gene therapy is a crucial plot element in the video game Metal Gear Solid, where it has been used to enhance the battle capabilities of enemy soldiers.

Publications

Molecular Therapy is the official journal of the American Society of Gene Therapy, and is a rapid-publication, peer-reviewed journal covering all aspects of human gene, cell, protein and nucleic acid therapy.

See also

- Antisense therapy
- Genetic engineering

Further reading

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Chemopreventive agents

Chemoprophylaxis refers to the administration of a medication for the purpose of preventing disease. Antibiotics, for example, may be administered to patients with disorders of immune system function to prevent infection (particularly opportunistic infection). Antibiotics may also be administered to healthy individuals to limit the spread of an epidemic, or to patients who have repeated infections (such as urinary tract infections) to prevent recurrence.

In some cases, chemoprophylaxis is initiated to prevent the spread of an existing disease in an individual to a new organ system, as when intrathecal chemotherapy is administered in patients with malignancy to prevent brain metastasis.

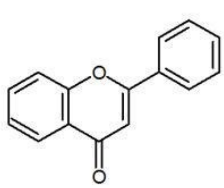
A related term is primary prevention, in which measures are undertaken to prevent the onset of disease in individuals who are susceptible (as when patients receive aspirin or statins to delay the development of coronary artery disease).

The use of chemoprophylaxis is limited primarily by two factors:

- All medications have the potential to cause side effects. In general, chemoprophylaxis should be initiated only when the benefits of treatment outweigh the risks.
- The cost associated with chemoprophylaxis may be prohibitive, particularly when the cost of treatment is high or the incidence of the target disease is low. Many forms of chemoprophylaxis are therefore not cost-effective.

Chemoprophylaxis is also used to treat several different varieties of meningococcal infections for close contact exposure to Neisseria menigitidis.

Flavonoids



Molecular structure of flavone

The term *flavonoid* refers to a class of plant secondary metabolites based around a phenylbenzopyrone structure. Flavonoids are most commonly known for their antioxidant activity. Flavonoids are also commonly referred to as *bioflavonoids* in the media – these terms are equivalent and interchangeable, since all flavonoids are biological in origin.

Biosynthesis

Flavonoids are synthesized by the phenylpropanoid pathway in which the amino acid phenylalanine is used to produce 4-coumaryl-CoA. This can be combined with malonyl-CoA to yield the true backbone of flavonoids, a group of compounds called chalcones. Ring-closure of these compounds results in the familiar form of flavonoids, a three-ringed structure (polyphenols). The metabolic pathway continues through a series of enzymatic modifications to yield flavanones ’ dihydroflavonols ’ anthocyanins. Along this pathway many products can be formed, including the flavonols, flavan-3-ols, proanthocyanidins (tannins) and a host of other polyphenolics.

Biological effects

Flavonoids are widely distributed in plants fulfilling many functions including producing yellow or red/blue pigmentation in flowers and protection from attack by microbes and insects. The widespread distribution of flavonoids, their variety and their relatively low toxicity compared to other active plant compounds (for instance alkaloids) mean that many animals, including humans, ingest significant quantities in their diet. Flavonoids have been found in high concentrations in butterflies and moths sequestered from dietary intake at the larval stage and then stored in adult tissues.

Flavonoids have been referred to as "nature's biological response modifiers" because of strong experimental evidence of their inherent ability to modify the body's reaction to allergens, viruses, and carcinogens. They show anti-allergic, anti-inflammatory[1] , anti-microbial and anti-cancer activity. In addition, flavonoids act as powerful antioxidants, protecting against oxidative and free radical damage.

Consumers and food manufacturers have become interested in flavonoids for their medicinal properties, especially their potential role in the prevention of cancers and cardiovascular disease. The beneficial effects of fruit, vegetables, and tea or even red wine have been attributed to flavonoid compounds rather than to known nutrients and vitamins.

Important flavonoids

Quercetin

Quercetin is a flavonoid that forms the "backbone" for many other flavonoids, like rutin. In studies, quercetin is found to be the most active of the flavonoids, and many medicinal plants owe much of their activity to their high quercetin content. Quercetin has demonstrated significant anti-inflammatory activity because of direct inhibition of several initial processes of inflammation. For example, it inhibits both the manufacture and release of histamine and other allergic/inflammatory mediators. In addition, it exerts potent antioxidant activity and vitamin C-sparing action.

Oligomeric proanthocyanidins

Proanthocyanidins extracts demonstrate a wide range of pharmacological activity. Their effects include increasing intracellular vitamin C levels, decreasing capillary permeability and fragility, scavenging oxidants and free radicals, and inhibiting destruction of collagen, the most abundant protein in the body.

Epicatechin

Epicatechin improves blood flow and thus seems good for cardiac health. Cocoa, the major ingredient of dark chocolate, is loaded with epicatechin and has been found to have nearly twice the antioxidant content of red wine and up to three times that of green tea.

Important dietary sources

Good sources of flavonoids include all citrus fruits, berries, onions, parsley, legumes, green tea, red wine, seabuckthorn, and dark chocolate (that with a cocoa content of seventy percent or greater).

Citrus

The citrus bioflavonoids include hesperidin, quercetin, rutin (a sugar of quercetin), and tangeritin. In addition to possessing antioxidant activity and an ability to increase intracellular levels of vitamin C, rutin and hesperidin exert beneficial effects on capillary permeability and blood flow. They also exhibit some of the anti-allergy and anti-inflammatory benefits of quercetin. Quercetin can also inhibit reverse transcriptase, part of the replication process of retroviruses (Spedding et al. 1989). The therapeutical relevance of this inhibition has not been established. Hydroxyethylrutosides (HER) have been used in the treatment of capillary permeability, easy bruising, hemorrhoids, and varicose veins.

Green Tea

Green tea polyphenols are potent antioxidant compounds that have demonstrated greater antioxidant protection than vitamins C and E. Green tea may also increase the activity of antioxidant enzymes. Green tea polyphenols may inhibit cancer by blocking the formation of cancer-causing compounds and suppressing the activation of carcinogens. The major polyphenols in green tea are *flavonoids* (catechin, epicatechin, epicatechin gallate, epigallocatechin gallate(EGCG), and proanthocyanidins).

Though both green tea and black tea are derived from the same plant (Camellia sinensis), they possess different antioxidants. In producing black tea the leaves are allowed to oxidize, during which enzymes present in the tea convert many polyphenols to larger molecules with different biological effects. However, green tea is produced by lightly steaming the fresh-cut leaf, which inactivates these enzymes, and oxidation does not occur.

Availability through microorganisms

A number of recent research articles have demonstrated the efficient production of flavonoid molecules from recombinant microorganisms. Such an approach opens the possibility of readily producing these compounds using renewable feedstocks and thus increasing the availability of rare flavonoid molecules for human and animal feed through dietary supplements.

Subgroups

Over 5000 naturally occurring flavonoids have been characterized from various plants. They have been classified according to their chemical structure, and are usually subdivided into 6 subgroups[2]:

- *Flavones* use the 2-phenylbenzopyrone skeleton shown *without a hydroxyl group at the 3 position*.

Examples: Luteolin, Apigenin

- *Flavonols* use the 2-phenylbenzopyrone skeleton shown *with a hydroxyl group at the 3 position*.

Examples: Quercetin, Kaempferol, Myricetin, Isorhamnetin, Pachypodol, Rhamnazin

- **Flavanones** use the 2-phenylbenzopyrone skeleton with the saturated 2,3 bond and without a hydroxyl group at the 3 position.

Examples: Hesperetin, Naringenin, Eriodictyol

- *Flavan-3-ols* use the 2-phenylbenzopyran skeleton

Examples: (+)-Catechin, (+)-Gallocatechin, (-)-Epicatechin, (-)-*Epigallocatechin, (-)-Epicatechin 3-gallate, (-)-Epigallocatechin 3-gallate, Theaflavin, Theaflavin 3-gallate, Theaflavin 3'-gallate, Theaflavin 3,3' digallate, Thearubigins

- *Isoflavones* use the 3-phenylbenzopyrone skeleton

Examples: Genistein, Daidzein, Glycitein

- Anthocyanidins.

Examples: Cyanidin, Delphinidin, Malvidin, Pelargonidin, Peonidin, Petunidin

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Anthocyanins

Anthocyanins (from Greek: ½¸ÌÂ (anthos) = flower + ºÅ±½ÌÂ (kyanos) = blue) are water-soluble vacuolar flavonoid pigments that appear red to blue, according to pH. They are synthesized exclusively by organisms of the plant kingdom, and have been observed to occur in all tissues of higher plants, providing color in leaves, stems, roots, flowers, and fruits.

Function

In flowers, anthocyanin pigments function as pollinator attractants, and in fruits, the colorful skins attract animals which will eat the fruits and disperse the seeds. In photosynthetic tissues (such as leaves), anthocyanins have been shown to act as a "sunscreen", protecting cells from photo-damage by absorbing UV and blue-green light, thereby protecting the tissues from photoinhibition, or high light stress. This has been shown to occur in red juvenile leaves, autumn leaves, and broad-leaved evergreen leaves that turn red during the winter. It is also thought that red coloration of leaves may camouflage leaves from herbivores blind to red wavelengths, or signal unpalatability to herbivores, since anthocyanin synthesis often coincides with synthesis of unpalatable phenolic compounds.

In addition to their role as light-attenuators, anthocyanins also act as powerful antioxidants, helping to protect the plant from radicals formed by UV light and during metabolic processes. This antioxidant property is conserved even after consumption by another organism, which is another reason why fruits and vegetables with red skins and tissues are a nutritious food source.

Occurrence

foodstuff - Anthocyanin in mg per 100 g foodstuff

blackcurrant 190-270

chokeberry 200-1000

aubergine 750

orange ~200

blackberry ~115

vaccinium 80-420

raspberry 10-60

cherry 350-400

redcurrant 80-420

red grape 30-750

red wine 24-35

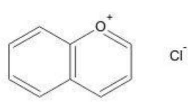
Not all land plants contain anthocyanin and in the Caryophyllales, Cactus and Galium mollugo they are replaced by betacyanins.

Anatomically, anthocyanins are found mostly in flowers and fruits but also in leaves, stems, and roots. In these parts they are found predominantly in outer cell layers such as the epidermis and peripheral mesophyll cells. The amounts are relatively large: one kilogram of blackberry for example contains approximately 1.15 gram, and red and black legumes can contain 20 gram per 1 kg. Other plants rich in anthocyanins are blackcurrant, chokeberry, cherry, eggplant, blue grape, Vaccinium and red cabbage and also the Usambara-violet. Anthocyanins are less abundant in banana, asparagus, pea, fennel, pear and potato. Most frequent in nature are the glycosides of cyanidin, delphinidin, malvidin, pelargonidin, peonidin and petunidin. Roughly 2% of all hydrocarbons fixated in photosynthesis are converted into flavonoids and their derivatives such as the anthocyanins. This is no less than 10[9] tons per year.

In plants anthocyanins are present together with other natural pigments like the closely chemically related flavonoids, carotenoids, anthoxanthins and betacyanins.

In still relatively young plants or new growth, where chlorophyll and wax production has not yet begun and which would be unprotected from UV light, anthocyanin production increases. Parts or even the whole plant are colored by these "juvenile anthocyanins," and thereby protected from damage. As soon as chlorophyll production begins, the production of the anthocyanin dye is reduced. The build-up of anthocyanin in plants is specific to the plant type, since it depends on the soil conditions, light, warmth and plant type and/or sort. Plants that have only a single anthocyanin as pigment is extremely rare, but occurs nevertheless. The absence or particularly strong prevalence for a certain anthocyanin in a plant is due to genetic circumstances.

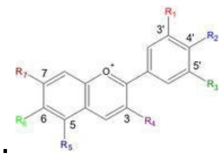
Structure



Benzopyrylium salts, Chloride as counterion

The pigment components of the anthocyanidins, the sugar-free anthocyanins, can be identified based on the structure of a large group of polymethine dye, as salt derivative of benzopyrylium (a cationic form of benzopyran, i.e an oxygen-containing heterocycle pyran fused to a benzene ring). The pyran ring in anthocyanin is connected to a phenyl group at the 2-position, which can carry different substituents. The counterion for the cationic oxygen in the pyran ring is mostly chloride. With this positive charge the anthocyanins differ from other flavonoids. The anthocyanins, anthocyanidins with sugar group, are mostly 3-glucosides of the anthocyanidins. In red wine, especially after maturation, many derivatives of the anthocyanins can be found.

The anthocyanins are subdivided into the sugar-free anthocyanidine aglycons and the anthocyanin glycosides. They are considered secondary metabolites and allowed as a food additive with E number 163. As of 2003 more than 400 anthocyanins had been reported[1] while more recent literature (early 2006), puts the number at more than 550 different anthocyanins. The difference in chemical structure that occurs in response to changes in pH is the reason why anthocyanins are often used as pH indicator, as they change from red in acids to blue in bases.



. Anthocyanin ground structure: the flavylium cation

Anthocyanidin	R_1	R_2	R_3	R_4	R_5	R_6	R_7
Aurantinidin	-H	-OH	-H	-OH	-OH	-OH	-OH
Cyanidin	-OH	-OH	-H	-OH	-OH	-H	-OH
Delphinidin	-OH	-OH	-OH	-OH	-OH	-H	-OH
Europinidin	$-OCH_3$	-OH	-OH	-OH	$-OCH_3$	-H	-OH
Luteolinidin	-OH	-OH	-H	-H	-OH	-H	-OH
Pelargonidin	-H	-OH	-H	-OH	-OH	-H	-OH
Malvidin	$-OCH_3$	-OH	$-OCH_3$	-OH	-OH	-H	-OH
Peonidin	$-OCH_3$	-OH	-H	-OH	-OH	-H	-OH
Petunidin	-OH	-OH	$-OCH_3$	-OH	-OH	-H	-OH
Rosinidin	$-OCH_3$	-OH	-H	-OH	-OH	-H	$-OCH_3$

Biosynthesis

Anthocyanin pigments are assembled from two different streams of chemical raw materials in the cell: both starting from the C2 unit acetate (or acetic acid) derived from photosynthesis, one stream involves the shikimic acid pathway to produce the amino acid phenylalanine. The other stream (the acetic acid pathway) produces 3 molecules of malonyl-Coenzyme A, a C3 unit. These streams meet and are coupled together by the enzyme chalcone synthase (CHS), which forms an intermediate chalcone via a polyketide folding mechanism that is commonly found in plants. The chalcone is subsequently isomerized by the enzyme chalcone isomerase (CHI) to the prototype pigment naringenin, which is subsequently oxidized by enzymes such as flavanone hydroxylase (FHT or F3H), flavonoid 3' hydroxylase and flavonoid 3' 5'-hydroxylase. These oxidation products are further reduced by the enzyme dihydroflavonol 4-reductase (DFR) to the corresponding leucoanthocyanidins. It was believed that leucoanthocyanidins are the immediate precursors of the next enzyme, a

dioxygenase referred to as anthocyanidin synthase (ANS) or leucoanthocyanidin dioxygenase (LDOX). It was recently shown however that flavan-3-ols, the products of leucoanthocyanidin reductase (LAR), are the true substrates of ANS/LDOX. The resulting, unstable anthocyanidins are further coupled to sugar molecules by enzymes like UDP-3-O-glucosyl transferase to yield the final relatively stable anthocyanins. More than five enzymes are thus required to synthesize these pigments, each working in concert. Any even minor disruption in any of the mechanism of these enzymes by either genetic or environmental factors would halt anthocyanin production.

Autumn Leaf Color

Many science text books incorrectly state that all autumn coloration (including red) is simply the result of breakdown of green chlorophyll, which unmasks the already-present orange, yellow, and red pigments (carotenoids, xanthophylls, and anthocyanins, respectively). While this is indeed the case for the carotenoids and xanthophylls (orange and yellow pigments), anthocyanins are not present until the leaf begins breaking down the chlorophyll, during which time the plant begins to synthesize the anthocyanin, presumably for photoprotection during nitrogen translocation.

Recent research

In December 2004 a peer-reviewed study at Michigan State University published by the American Chemical Society noted that anthocyanin could boost insulin production by up to 50%. However the study leader noted that despite the initial excitement, more study would be needed. Also in 2005, an article published in Applied and Environmental Microbiology demonstrated for the first time the biosynthesis of anthocyanins in bacteria.

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Polyphenol antioxidant

A *polyphenol antioxidant* is a type of antioxidant characterized by the presence of several phenol functions. In human health these compounds, numbering over 4000 distinct species, are thought to be instrumental in combating oxidative stress, a syndrome causative of some neurodegenerative diseases and some cardiovascular diseases.

The main source of polyphenol antioxidants is nutritional, since they are found in a wide array of phytonutrient-bearing foods. For example, most legumes; fruits such as apples,

blackberries, cantaloupe, cherries, cranberries, grapes, pears, plums, raspberries, and strawberries; and vegetables such as broccoli, cabbage, celery, onion and parsley are rich in polyphenol antioxidants. Red wine, chocolate, green tea, olive oil, bee pollen and many grains are alternative sources. The principal benefit of ingestion of antioxidants seems to stem from the consumption of a wide array of phytonutrients; correspondingly, the role of dietary supplements as a method of realizing these health benefits is the subject of considerable discussion.

Biochemical regulation

The regulation chemistry consists of a polyphenol antioxidant's ability to scavenge free radicals and up-regulate certain metal chelation reactions. That is to say various reactive oxygen species must be continually removed from cells to maintain healthy metabolic function. Some specific free radicals affected are the reactive oxygen species singlet oxygen, peroxynitrite and hydrogen peroxide. Diminishing the concentrations of reactive oxygen species can have several benefits. Since reactive oxygen species are linked to mobilization of ion transport systems, they are known to have roles in oxidative signalling. In particular, platelets involved in wound repair and blood homeostasis can release reactive oxygen species to recruit platelets to sites of injury. These also provide a link to the adaptive immune system via the recruitment of leukocytes. When polyphenol down-regulate reactive oxygen species formation, they also contribute to improved endothelial health through anti-inflammatory action.

Biological consequences

Occurrence of an abundance of polyphenol antioxidants is associated with several salutary effects in higher animal species:

- Reduction in inflammatory effects such as coronary artery disease[1][2] including specific medical research into the pathways of improved endothelial health via downregulation of oxidative LDL.[3]
- More generally the tea polyphenol (medically known as TP) antioxidant epigallocatechin gallate, has been shown to reduce reactive oxygen species levels in vivo.[4] Reactive oxygen species are important markers for inflammatory diseases.
- Some polyphenol antioxidants, such as resveratrol, inhibit occurrence and/or growth of mammalian tumors.[5]
- A variety of other beneficial health effects have been attributed to consumption of foods rich in polyphenolic antioxidants. Among these salutary effects discussed are anti-aging consequences such as slowing the process of skin wrinkling.[6] For some of the side-benefits (such as prevention of peripheral artery disease), further research is continuing to clarify the role polyphenol antioxidants may have.[7][8]

Difficulty in analyzing effects of specific chemicals

It is inherently difficult to evaluate the medical effects of specific polyphenolic antioxidants, since such a large number of individual compounds may occur even in a single food. For example, over sixty different chemically distinct flavonoids are known to occur in a given red wine. Numerous scientific studies have been conducted to attempt to arrive at one consistent index for food antioxidant power. Since it has been proved that the dietary intake of compounds having antioxidant activity is medically important, various chemical, biological, and electrochemical methods have been proposed to evaluate the antioxidant power of compounds such as polyphenols. Wine, although nonessential, has a high polyphenol content up to two to three grams per liter in red wines obtained by traditional maceration. The polyphenol content of wines is usually evaluated by the Folin-Ciocalteu reagent, which provides an appropriate response to the requirements of wine manufacturers. Statistical least squares analysis has been conducted to demonstrate the Folin method correlates well with alternative chemical and biological procedures for determining antioxidant potential.[9] Therefore, there is some reason to believe more universally accepted protocols may be forthcoming to permit quantitative evaluation of antioxidant strength of polyphenol antioxidant compounds.

Other more detailed chemical reseach has been conducted elucidating the difficulty of isolating individual polyphnolic antioxidants. Fajardo-Lirai et al. have demonstrated that significant variation in polyphenol content among various brands of tea can explain[10] the inconsistency in previous epidemiological studies that have tried to correlate beneficial health effects of polyphenol antioxidants using specific green tea blends. The Oxygen Radical Absorbance Capacity (ORAC) test is a possible emerging standard by which science measures antioxidant power in foods and dietary supplements

Practical aspects of dietary polyphenol antioxidants

There is debate regarding the total body absorption of dietary intake of polyphenolic compounds. While individual studies seem to demonstrate the favourable health effects of certain specific polyphenols, more research is needed to understand the interactions between a variety of these chemicals acting in concert within the human body. In particular there is evidence that some combinations of foods may inhibit efficient intestinal transfer of certain polyphenol antioxidants; refined sugars, for example, have been shown to impede this uptake under certain circumstances.[11] Furthermore caution should be exercised in attempting diets depending largely on dietary supplements as opposed to a broad array of food sources, since the quality and concentrations of beneficial chemicals in some commercial products is subject to question, given lack of Food and Drug Administration (FDA) regulation.

Topical application of polyphenol antioxidants

There is some data that reactive oxygen species play a role in the process of aging. The skin is exposed to various exogenous sources of oxidative stress, including ultraviolet radiation. These spectral components are generally viewed as responsible for the extrinsic type of skin aging, sometimes termed photo-aging. It has been shown not only that increased levels of protective low molecular weight antioxidants through a diet rich in phytochemicals,

but also by direct topical dermal application[12] have proved that a few low molecular weight antioxidants, notably vitamins C and E, ascorbate and tocopherol, as well as lipoic acid, exert protective effects against oxidative stress. However, controlled long-term studies on the efficacy of low molecular weight antioxidants in the prevention or treatment of skin aging in humans is lacking.

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12. ^ Clin Exp Dermatol. 2001 Oct;26(7):578-82 There is increasing evidence that reactive oxygen species play a pivotal role in the process of aging. The skin, as the outermost barrier of the body, is exposed to various exogenous sources of oxidative stress, in particular UV-irradiation. These are believed to be responsible for the extrinsic type of skin aging, termed photo-aging. It therefore seems possible to increase levels of protective low molecular may produce anti-aging effects on human skin. Indeed, various in vitro and animal studies

Tannins

Tannins are astringent, bitter-tasting plant polyphenols that bind and precipitate proteins. The term tannin refers to the source of tannins used in tanning animal hides into leather; however, the term is applied to any large polyphenolic compound containing sufficient hydroxyls and other suitable groups (such as carboxyls) to form strong complexes with proteins and other macromolecules. Tannins have molecular weights ranging from 500 to over 20,000.

Tannins are usually divided into hydrolyzable tannins and condensed tannins (proanthocyanidins). At the center of a hydrolyzable tannin molecule, there is a polyol carbohydrate (usually D-glucose). The hydroxyl groups of the carbohydrate are partially or totally esterified with phenolic groups such as gallic acid (in gallotannins) or ellagic acid (in ellagitannins). Hydrolyzable tannins are hydrolyzed by weak acids or weak bases to produce carbohydrate and phenolic acids. Condensed tannins, also known as proanthocyanidins, are polymers of 2 to 50 (or more) flavonoid units that are joined by carbon-carbon bonds, which are not susceptible to being cleaved by hydrolysis. While hydrolyzable tannins and most condensed tannins are water soluble, some very large condensed tannins are insoluble.

Tannins may be employed medicinally in antidiarrheal, hemostatic, and antihemorrhoidal compounds. Also, they produce different colors with ferric chloride (either blue, blue black, or green to greenish black) according to the type of tannin.

Examples of gallotannins are the esters of tannic acid (C76H52O46) with glucose, found in the leaves and bark of many plant species.

Tea

The tea plant (Camellia sinensis) is an example of a plant with a naturally high tannin content. Green tea leaves are unquestionably a major plant source of tannins, as they not only contain the tannic and gallic acid groups, but also a proanthocyanidin (a type of flavanol) named prodelphinidin. When any type of tea leaf is steeped in hot water for an excessively long time period it brews a "tart" (astringent) flavor that is characteristic of tannins (and other components). New varieties of Camellia sinensis have been specifically bred for a lower tannin content. If ingested in excessive quantities, tannins inhibit the absorption of minerals such as iron into the body. This is because tannins are metal ion chelators, and tannin-chelated metal ions are not bioavailable.

Wine

Tannins (mainly condensed tannins) are also found in wine, particularly red wine. Tannins in wine can come from many sources and the tactile properties differ depending on the source. Tannins in grape skins and seeds (the latter being especially harsh) tend to be more noticeable in red wines, which are fermented while in contact with the skins and seeds. Tannins extracted from grapes are condensed tannins, which are polymers of procyanidin monomers. Hydrolysable tannins are extracted from the oak wood the wine is aged in. Hydrolysable tannins are more easily oxidised than condensed tannins.

Modern winemakers take great care to minimize undesirable tannins from seeds by crushing grapes gently to extract their juice. Pressing the grapes results in press wine which is more tannic and might be kept separately. Wines can also take on tannins if matured in oak or wood casks with a high tannin content. Tannins play an important role in preventing oxidation in aging wine and appear to polymerize and make up a major portion of the sediment in wine.

Pomegranates

Pomegranates contain a diverse array of tannins, particularly hydrolysable tannins. The most abundant of pomegranate tannins are called punicalagins. Punicalagins have a molecular weight of 1038 and are the largest molecule found intact in rat plasma after oral ingestion (Biomed. Pharmacother. 2002, 56, 276-82) and were found to show no toxic effects in rats who were given a 6% diet of punicalagins for 37 days. (J. Agric. Food Chem. 2003, 51, 3493-3501). Punicalagins are also found to be the major component responsible for pomegranate juice's antioxidant and health benefits (J Agric Food Chem 2000 48 (10) 4581-89).

Several dietary supplements and nutritional ingredients are available that contain extracts of whole pomegranate and/or are standardized to punicalagins, the marker compound of pomegranate. Extracts of pomegranate are also 'Generally Recognized As Safe' (GRAS) by the United States. It has been recommended to look for pomegranate ingredients that mimic the polyphenol ratio of the fruit, as potent synergistic effects have been observed in 'natural spectrum' extracts, especially pomegranate concentrate normalized to punicalagins (J Nutr Biochemistry 2005 (16) 360-367).

Leather

Tannins are an important ingredient in the process of tanning leather. Oak bark has traditionally been the primary source of tannery tannin, though synthetic tanning agents are also in use today.

Turmeric

Scientific classification

Kingdom: Plantae
Division: Magnoliophyta
Class: Liliopsida
Subclass: Zingiberidae
Order: Zingiberales
Family: Zingiberaceae
Genus: Curcuma
Species: *C. longa*

Binomial name *Curcuma longa*

Turmeric (Curcuma longa, also called *tumeric* or *kunyit* in some Asian countries[1]) is a spice commonly used in curries and other South Asian cuisine. Its active ingredient is curcumin. It is a significant ingredient in most commercial curry powders. Turmeric is also used to give a yellow color to some prepared mustards, canned chicken broth, and other foods (often as a much cheaper replacement for saffron). It makes a poor fabric dye as it is not very lightfast (the degree to which a dye resists fading due to light exposure).

Turmeric, a representative of plant genus Curcuma, is a member of the ginger family, Zingiberaceae.

In Ayurvedic medicine, turmeric is thought to have many healthful properties. It is taken in some Asian countries as a dietary supplement, which allegedly helps with stomach problems and other ailments. It is popular as a tea in Okinawa, Japan. It is currently being investigated for possible benefits in Alzheimer's disease, cancer and liver disorders.

Sangli, a town in the southern part of the Indian state of Maharashtra, is the largest and most important trading centre for turmeric in Asia or perhaps in the entire world.

Food additive

Turmeric (coded as E100 when used as a food additive) is used in product systems that are packaged to protect them from sunlight. The oleoresin is used for oil-containing products. The curcumin/polysorbate solution or curcumin powder dissolved in alcohol is used for water containing products. Over-colouring, such as in pickles, relishes and mustard, is sometimes used to compensate for fading.

Turmeric has found application in canned beverages, baked products, dairy products, ice cream, yogurts, yellow cakes, biscuits, popcorn-color, sweets, cake icings, cereals, sauces, gelatines, direct compression tablets, etc. In combination with Annatto (E160b) it has been used to colour cheeses, dry mixes, salad dressings, winter butter and margarine.

Medicine

The medicinal properties of the turmeric have for millennia been known to the ancient Indians and have been expounded in the Ayurvedic texts. It is only in recent years that Western scientists have increasingly recognised the medicinal properties of turmeric. According to a 2005 article in the Wall Street Journal titled, "Common Indian Spice Stirs Hope," research activity into curcumin, the active ingredient in turmeric, is exploding. Two hundred and fifty-six curcumin papers were published in the past year according to a search of the U.S. National Library of Medicine. Supplement sales have increased 35% from 2004, and the U.S. National Institutes of Health has four clinical trials underway to study curcumin treatment for pancreatic cancer, multiple myeloma, Alzheimer's, and colorectal cancer.

A 2004 UCLA-Veterans Affairs study involving genetically altered mice suggests that curcumin, the active ingredient in turmeric, might inhibit the accumulation of destructive beta amyloids in the brains of Alzheimer's disease patients and also break up existing plaques. "Curcumin has been used for thousands of years as a safe anti-inflammatory in a variety of ailments as part of Indian traditional medicine," Gregory Cole, Professor of medicine and neurology at the David Geffen School of Medicine at UCLA said.

Another 2004 study conducted at Yale University involved oral administration of circumin to mice homozygous for the most common allele implicated in cystic fibrosis. Treatment with circumin restored physiologically-relevant levels of protein function.

Recent studies have shown that turmeric can be effective in fighting a number of STDs including chlamydia and gonorrhea.

Investigations into the low incidence of colorectal cancer amongst ethnic groups with a large intake of curries compared with the indigenous population have suggested that some active ingredients of turmeric may have anti-cancer properties.

Anti-tumoral effects against melanoma cells have been demonstrated.

Second-stage trials of a turmeric-based drug as a possible treatment for cancer are currently underway. However, according to recent research results, the component curcumin causes degradation of the human protein p53. p53 is responsible for removing damaged cells that are likely to become tumors, suggesting curcumin could accelerate tumor development.

Consuming large doses is not recommended in cases of gallstones, obstructive jaundice, acute bilious colic and toxic liver disorders.

Curry Pharmaceuticals, based in North Carolina, is studying the use of a curcumin cream for psoriasis treatment. Another company is already selling a cream based on curcumin called "Psoria-Gold," which shows anecdotal promise of treating the disease.

A recent study involving mice has shown that turmeric slows the spread of breast cancer into lungs and other body parts. Turmeric also enhances the effect of taxol in reducing metastasis of breast cancer.

It is also said that turmeric can strengthen the blood-brain barrier against attacks that result from auto-immune diseases (such as Multiple sclerosis).

In the November 2006 issue of Arthritis & Rheumatism, a study was published that showed the effectiveness of turmeric in the reduction of joint inflammation, and recommended clinical trials as a possible treatment for the alleviation of arthritis symptoms.

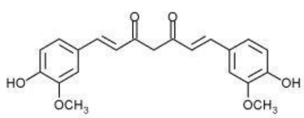
Cosmetics

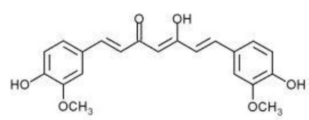
Turmeric is currently used in the formulation of some sun screens. Turmeric paste is used by Indian women to keep them free of superfluous hair.

The Government of Thailand is funding a project to extract and isolate tetrahydrocurcuminoids (THC) from turmeric. THCs are colorless compounds that might have antioxidant and skin lightening properties and might be used to treat skin inflammations, making these compounds useful in cosmetics formulations.

Chemistry

The active substance of turmeric is the polyphenol *curcumin*, also known as C.I. 75300, or Natural Yellow 3. Systematic chemical name is (1E,6E)-1,7-bis(4-hydroxy-3-methoxyphenyl)-1,6-heptadiene-3,5-dione. It can exist at least in two tautomeric forms, keto and enol. The keto form is preferred in solid phase and the enol form in solution.


Curcumin Keto form


Curcumin Enol form

Notes

1. ^ Turmeric is known by different names in different languages. Some examples include:
    - "Arishina" in Kannada
    - "Halad" in Marathi
    - "Haldi" in Hindi and Gujarati.
    - "Holood" in Bengali.
    - "®žÍš^{3}Í" (manjal) in Tamil.
    - "Pasupu" in Telugu.
    - "ÜÄ" (jiang huang) in Chinese.

Medicinal chemistry

Medicinal or *pharmaceutical chemistry* is a scientific discipline at the intersection of chemistry and pharmacy involved with designing, synthesizing and developing pharmaceutical drugs. Medicinal chemistry involves the identification, synthesis and development of new chemical entities suitable for therapeutic use. It also includes the study of existing drugs, their biological properties, and their quantitative structure-activity relationships (QSAR). Pharmaceutical chemistry is focused on quality aspects of medicines and aims to assure fitness for the purpose of medicinal products.

Medicinal chemistry is a highly interdisciplinary science combining organic chemistry with biochemistry, computational chemistry, pharmacology, molecular biology, statistics, and physical chemistry.

Process of drug discovery

Discovery

The first step of drug discovery involves the identification of new active compounds, often called "hits", which are typically found by screening many compounds for the desired biological properties. These hits can come from natural sources, such as plants, animals, or fungi. More often, the hits can come from synthetic sources, such as historical compound collections and combinatorial chemistry.

Recent developments in robotics and miniaturization have greatly accelerated and automated the screening process. Typically, a company will assay over 100,000 individual compounds before moving to the optimization step.

Optimization

The second step of drug discovery involves the synthetic modification of the hits in order to improve the biological properties of the compound pharmacophore. The quantitative structure-activity relationship of the pharmacophore play an important part in finding "lead compounds", which exhibit the most potency, most selectivity, best pharmacokinetics and least toxicity.

Development

The final step involves the rendering the "lead compounds" suitable for use in clinical trials. This involves the optimization of the synthetic route for bulk production, and the preparation of a suitable drug formulation.

See also

- Pharmacology
- Pharmacodynamics
- Pharmacokinetics
- Pharmaceutical company

Bioavailability

In pharmacology, *bioavailability* is used to describe the fraction of an administered dose of medication that reaches the systemic circulation, one of the principal pharmacokinetic properties of drugs. By definition, when a medication is administered intravenously, its bioavailability is 100%. However, when a medication is administered via other routes (such as by mouth), its bioavailability decreases (due to incomplete absorption and first-pass metabolism). Bioavailability is one of the essential tools in pharmacokinetics, as bioavailability must be considered when calculating dosages for non-intravenous routes of administration.

Definition

Bioavailability is a measurement of the rate and extent of a therapeutically active drug that reaches the systemic circulation and is available at the site of action.[1]

It is expressed as the letter F.

Absolute bioavailability

Absolute bioavailability measures the availability of the active drug in systemic circulation after non-intravenous administration (i.e., after oral, rectal, transdermal, subcutaneous administration).

In order to determine absolute bioavailability of a drug, a pharmacokinetic study must be done to obtain a plasma drug concentration vs time plot for the drug after both intravenous (IV) and non-intravenous administration. The absolute bioavailability is the dose-corrected area under curve (AUC) non-intravenous divided by AUC intravenous. For example, the formula for calculating F for a drug administered by the oral route (po) is given below.

$$F = \frac{[AUC]_{po} * dose_{IV}}{[AUC]_{IV} * dose_{po}}$$

Therefore, a drug given by the intravenous route will have an absolute bioavailability of 1 (F=1) while drugs given by other routes usually have an absolute bioavailability of less than one.

Relative bioavailability

This measures the bioavailability of a certain drug when compared with another formulation of the same drug, usually an established standard, or through administration via a different route. When the standard consists of intravenously administered drug, this is known as absolute bioavailability.

$$relative\ bioavailability = \frac{[AUC]_A * dose_B}{[AUC]_B * dose_A}$$

Factors influencing bioavailability

The absolute bioavailability of a drug, when administered by an extravascular route, is usually less than one (i.e. F<1). Various physiological factors reduce the availability of drugs prior to their entry into the systemic circulation,

Such factors may include, but are not limited to:

- poor absorption from the gastrointestinal tract
- degradation or metabolism of the drug prior to absorption
- hepatic first pass effect

Each of these factors may vary from patient to patient, and indeed in the same patient over time. Whether a drug is taken with or without food will affect absorption, other drugs taken concurrently may alter absorption and first-pass metabolism, intestinal motility alters the dissolution of the drug and may affect the degree of chemical degradation of the drug by intestinal microflora. Disease states affecting liver metabolism or gastrointestinal function will also have an effect.

References

1. ^ Shargel, L.; Yu, A.B. (1999). Applied biopharmaceutics & pharmacokinetics (4th ed.). New York: McGraw-Hill. ISBN 0-8385-0278-4

Drug design

Drug design is the approach of finding drugs by design, based on their biological targets. Typically a drug target is a key molecule involved in a particular metabolic or signalling pathway that is specific to a disease condition or pathology, or to the infectivity or survival of a microbial pathogen.

Some approaches attempt to stop the functioning of the pathway in the diseased state by causing a key molecule to stop functioning. Drugs may be designed that bind to the active region and inhibit this key molecule. However these drugs would also have to be designed in such a way as not to affect any other important molecules that may be similar in appearance to the key molecules. Sequence homologies are often used to identify such risks.

Other approaches may be to enhance the normal pathway by promoting specific molecules in the normal pathways that may have been affected in the diseased state.

The structure of the drug molecule that can specifically interact with the biomolecules can be modeled using computational tools. These tools can allow a drug molecule to be constructed within the biomolecule using knowledge of its structure and the nature of its active site. Construction of the drug molecule can be made inside out or outside in depending on whether the core or the R-groups are chosen first. However many of these approaches are plagued by the practical problems of chemical synthesis.

Newer approaches have also suggested the use of drug molecules that are large and proteinaceous in nature rather than as small molecules. There have also been suggestions to make these using mRNA. Gene silencing may also have therapeutical applications.

Rational drug design

Unlike the historical method of drug discovery, by trial-and-error testing of chemical substances on animals, and matching the apparent effects to treatments, rational drug design begins with a knowledge of specific chemical responses in the body or target organism, and tailoring combinations of these to fit a treatment profile. Due to the complexity of the drug design process two terms of interest are still Serendipity and bounded rationality.

An important case study in rational drug design is imatinib, a tyrosine kinase inhibitor designed specifically for the bcr-abl fusion protein that is characteristic for Philadelphia chromosome-positive leukemias (chronic myelogenous leukemia and occasionally acute lymphocytic leukemia). Imatinib is substantially different from previous drugs for cancer, as most agents of chemotherapy simply target rapidly dividing cells, not differentiating between cancer cells and other tissues.

Examples of designed drugs

- Cimetidine, the prototypical H^2-receptor antagonist from which the later members of the class were developed
- Selective COX-2 inhibitor NSAIDs
- SSRIs (selective serotonin reuptake inhibitors), a class of antidepressants
- Zanamivir**, an** antiviral drug
- Enfuvirtide, a peptide HIV entry inhibitor

See also

- Drug discovery
- Bioinformatics
- Pharmaceutical company

Drug discovery

In medicine, biotechnology and pharmacology, *drug discovery* is the process by which drugs are discovered and/or designed.

In the past most drugs have been discovered either by identifying the active ingredient from traditional remedies or by serendipitous discovery. A new approach has been to understand how disease and infection are controlled at the molecular and physiological level and to target specific entities based on this knowledge.

The process of drug discovery involves the identification of candidates, synthesis, characterization, screening, and assays for therapeutic efficacy. Once a compound has shown its value in these tests, it will begin the process of drug development prior to clinical trials.

Despite advances in technology and understanding of biological systems, drug discovery is still a long process with low rate of new therapeutic discovery. Information on the human genome, its sequence and what it encodes has been hailed as a potential windfall for drug discovery, promising to virtually eliminate the bottleneck in therapeutic targets that has been one limiting factor on the rate of therapeutic discovery.[1] However, data indicates that "new targets" as opposed to "established targets" are more prone to drug discovery project failure in general.[2] This data corroborates some thinking underlying a pharmaceutical industry trend beginning at the turn of the twenty-first century and continuing today which finds more risk aversion in target selection among multi-national pharmaceutical companies.[3]

Targets: New and Established

The definition of "target" itself is something debated within the pharmaceutical industry. However, the distinction between a "new" and "established" target can be made without a full understanding of just what a "target" is. This distinction is typically made by pharmaceutical companies engaged in discovery and development of small molecule therapeutics.

"Established targets" are those for which there is a good scientific understanding, supported by a lengthy publication history, of both how the target functions in normal physiology and how it is involved in human pathology. This does not imply that the mechanism of action of drugs that are thought to act through a particular established targets is fully understood. Rather, "established" relates directly to the amount of background information available on a target, in particular functional information. The more such information is available, the less investment is (generally) required to develop a therapeutic directed against the target. The process of gathering such functional information is called "target validation" in pharmaceutical industry parlance. Established targets also include those that the pharmaceutical industry has had experience mounting drug discovery campaigns against in the past; such a history provides information on the chemical feasibility of developing a small molecular therapeutic against the target and can provide licensing opportunities and freedom-to-operate indicators with respect to small molecule therapeutic candidates.

In general, "new targets" are all those targets that are not "established targets" but which have been or are the subject of drug discovery campaigns. These typically include newly discovered proteins, or proteins whose function has now become clear as a result of basic scientific research.

The majority of targets currently selected for drug discovery efforts are proteins. Two classes predominate: G-protein-coupled receptors (or GPCRs) and protein kinases.

Screening and Design

The process of finding a new drug against a chosen target for a particular disease usually involves high-throughput screening (HTS), wherein large libraries of chemicals are tested for their ability to modify the target. For example, if the target is a novel GPCR, compounds will be screened for their ability to inhibit or stimulate that receptor (see antagonist and agonist): if the target is a protein kinase, the chemicals will be tested for their ability to inhibit that kinase.

Another important function of HTS is to show how selective the compounds are for the chosen target. The ideal is to find a molecule which will interfere with only the chosen target, but not other, related targets. To this end, other screening runs will be made to see whether the "hits" against the chosen target will interfere with other related targets - this is the process of *cross-screening*. Cross-screening is important, because the more unrelated targets a compound hits, the more likely that off-target toxicity will occur with that compound once it reaches the clinic.

It is very unlikely that a perfect drug candidate will emerge from these early screening runs. It is more often observed that several compounds are found to have some degree of activity, and if these compounds share common chemical features, one or more pharmacophores can then be developed. At this point, medicinal chemists will attempt to use structure-activity relationships (SAR) to improve certain features of the lead molecules:

- increase activity against the chosen target
- reduce activity against unrelated targets
- improve the "drug-like" or ADME properties of the molecule.

This process will require several iterative screening runs, during which, it is hoped, the properties of the new molecular entities will improve, and allow the favoured compounds to go forward to in vitro and in vivo testing for activity in the disease model of choice.

While HTS is a commonly used method for novel drug discovery, it is not the only method. It is often possible to start from a molecule which already has some of the desired properties. Such a molecule might be extracted from a natural product or even be a drug on the market which could be improved upon (so-called "me too" drugs). Other methods, such as virtual high throughput screening, where screening is done using computer-generated models and attempting to "dock" virtual libraries to a target, are also often used.

Another important method for drug discovery is drug design, whereby the biological and physical properties of the target are studied, and a prediction is made of the sorts of chemicals that might (eg.) fit into an active site. Novel pharmacophores can emerge very rapidly from these exercises.

Once a lead molecule series has been established with sufficient target potency and selectivity and favourable drug-like properties, one or two compounds will then be proposed for drug development. The best of these is generally called the "lead" compound, while the other will be designated as the "backup".

See also

- Drug development
- Drug design

- Bioinformatics
- Orphan drug
- Pharmaceutical company

Notes

1. ^ this requires substantiation with one or more reputable sources from the time of enthusiasm following "completion" of the human genome sequence
2. ^ Drug Discovery & Development, October 2005, Trend Watch: Success Rate by Discovery Phase, New and Established Target Projects
3. ^ Personal communication. this requires substantiation with one or more reputable sources reporting on industry trends in 2003–2005

References

- Shayne Cox Gad (2005), Drug Discovery Handbook, Wiley-Interscience, ISBN 0-471-21384-5
- Madsen U. (2002), Textbook of Drug Design and Discovery, CRC, ISBN 0-415-28288-8

Pharmacokinetics

Pharmacokinetics is a branch of pharmacology dedicated to the study of the time course of substances and their relationship with an organism or system. In practice, this discipline is applied mainly to drug substances, though in principle it concerns itself with all manner of compounds residing within an organism or system, such as nutrients, metabolites, endogenous hormones, toxins, etc. So, in basic terms, while pharmacodynamics explores what a drug does to the body, pharmacokinetics explores what the body does to the drug.

Absorption and disposition

Pharmacokinetics has been broadly divided into two categories of study: absorption and disposition. Once a drug is administered as a dose, these processes begin simultaneously.

Absorption

The process of absorption can be seen as increasing the amount of a compound or dose x introduced into a system. Absorption studies seek to define the rate of input, dx/dt, of the dose x. For example, a constant rate infusion, R, of a drug might be 1 mg/hr, while the integral over time of dx/dt is referred to as the extent of drug input, x(t), ie. the total amount of drug x administered up to that particular time t. Sometimes the drug is assumed to be absorbed

from the gastrointestinal tract in the form of a 1st order process with a 1st-order rate of absorption designated as Ka. Complex absorption profiles can be created by the use of controlled, extended, delayed or timed release of drugs from a dosage form.

Pharmacokinetics has many applications in drug therapy. By studying absorption -- the amount of a drug which gets into the system (bloodstream) following administration -- pharmacokinetics may guide the formulation of drug products. The amount of drug released from different formulations may vary; for example, two different tablets containing the same amount of drug chemical may not release the same amount into the bloodstream; a pharmacokinetic absorption study can determine whether or not the two tablets are equivalent and can be used interchangeably.

Disposition

Disposition is further subdivided into the study of the distribution, metabolism and elimination or excretion of a drug. Thus, pharmacokinetics is sometimes referred to as ADME.

The processes of disposition can be seen as clearing the system of a dose, or disposing of the dose. The disposition process distributes the compound or substance within the system, converts or metabolizes it, and eliminates the parent compound or products of the parent compound by passing them from the system into the urine, feces, sweat, exhalation or other routes of elimination. Sometimes compounds or their products may remain essentially indefinitely in the system by incorporation into the system.

The one-compartmental case

The functional form of the systemic clearance, Cls, of a drug x is equal to -(dx/dt)/c(t), where x(t) is the amount of drug present and c(t) is the observed drug concentration (for example in blood plasma). The units of clearance are given in terms of volume/time so that a generalized, well stirred volume is cleared of an amount of a substance x per unit of time following introduction into such volume. This well stirred volume V is the volume of distribution of a substance x (drug), and is essentially a proportionality constant between x(t) and c(t), such that x(t)=c(t)×V.

The total apparent systemic clearance Cls/(F×F*) is related to Cls, where F signifies bioavailability and F* signifies the first pass effect of an administered substance. If F and F* are known, the true systemic clearance, Cls, can be obtained by multiplying the observed apparent systemic clearance Cls/(F×F*) by F and F*. Cls is composed of many clearance components, two of the most common are the renal and non-renal components of clearance, Clr and Clnr, respectively, such that Cls = Clr + Clnr.

Modeling pharmacokinetic systems

Pharmacokinetics systems can be determined to be linear or nonlinear, and time-invariant or time-varying with respect to the mathematical modeling involved for any one of these processes.

Linear pharmacokinetic processes are generally the least complex to study and linear systems theory has been applied to modeling many pharmacokinetic systems when linearity can be assumed. One test of a drug's linearity is obtained by observing the AUC for several different administered doses. If the AUC varies directly with administered dose then the apparent systemic clearance of the drug, Cl, remains constant.

Nonlinear time-varying systems can be very difficult to solve and may have no closed-form solutions (meaning they have to be solved numerically on a case-by-case basis).

There is an extensive body of mathematical knowledge with many practitioners working in the area. This knowledge has roots in engineering, statistics, and medicine.

See also

- Pharmacodynamics
- Bioavailability
- Pharmaceutical company

Further reading

- "Pharmacokinetics" by Milo Gibaldi and Donald Perrier
- "Clinical Pharmacokinetics: Concepts and Applications" by Malcolm Rowland, Thomas N. Tozer

Pharmacodynamics

Pharmacodynamics is the study of the biochemical and physiological effects of drugs and the mechanisms of drug action and the relationship between drug concentration and effect. It is often summarily stated that pharmacodynamics is the study of what a drug does to the body, whereas pharmacokinetics is the study of what the body does to a drug.

Drug action

Desired activity

The desired activity of a drug is mainly due to one of the following:

- Cellular membrane disruption

Chemical reaction
Interaction with enzyme proteins
Interaction with structural proteins
Interaction with carrier proteins
Interaction with ion channels

- Ligand binding to receptors:
    - Hormone receptors
    - Neuromodulator receptors

Neurotransmitter receptors

General anesthetics are believed to work by disordering the neural membranes, thereby altering the Na+ influx. Antacids and chelating agents combine chemically in the body. Enzyme-substrate binding is a way to alter the production or metabolism of key endogenous chemicals, for example aspirin irreversibly inhibits the enzyme prostaglandin synthetase (cyclooxygenase) thereby preventing inflammatory response. Colchicine, a drug for gout, interferes with the function of the structural protein tubulin, while Digitalis, a drug still used in heart failure, inhibits the activity of the carrier molecule, Na-K-ATPase pump. The widest

class of drugs act as ligands which bind to receptors which determine cellular effects. Upon drug binding, receptors can elicit their normal action (agonist), blocked action (antagonist), or even action opposite to normal (anti-agonist).

In principle, a pharmacologist would aim for a certain plasma concentration of the drug for a desired level of response. In reality, there are many factors affecting this goal. Pharmacokinetic factors determine peak concentrations, and levels cannot be maintained with absolute consistency because of metabolic breakdown and excretory clearance. Genetic factors may exist which would alter metabolism or drug action itself, and a patient's immediate status may also affect indicated dosage.

Undesirable effects

Undesirable effects of a drug include:

- Increased probability of cell mutation (carcinogenic activity)
- A multitude of simultaneous assorted actions which may be deleterious
- Interaction (additive, multiplicative, or metabolic)
- Induced physiological damage, or abnormal chronic conditions

Receptor binding

The binding of ligands (drug) to receptors is governed by the law of mass action which relates the large-scale status to the rate of numerous molecular processes. The rates of formation and un-formation can be used to determine the equilibrium concentration of bound receptors. Although the receptors are fixed to a 2-dimensional membrane, an arbitrary control volume can be used to calculate the dissociation constant,

$$L + R \leftrightarrow L{\cdot}R \quad K_d = \frac{[L][R]}{[L{\cdot}R]}$$

where L=ligand, R=receptor, square brackets [] denote concentration. The fraction of bound receptors is found as $(1+[R]/[L{\cdot}R])^{-1}$, which can then be expressed using K_d as,

This expression is one way to consider the efficacy of a drug, in which the response may be directly proportional to the fraction of bound receptors. Often the response is determined as a function of log[L] to consider many orders of dosage range. It is useful to note that 50% of the receptors are bound when $[L]=K_d$.

A plot of the function for the bound fraction of receptors forms a typical model for the dose response of a drug. The graph shown represents the dose-response for two hypothetical receptor agonists, plotted in a semi-log fashion. The curve toward the left represents a higher potency (potency arrow does not indicate direction of increase) since lower concentrations are needed for a given response. The efficacy increases as a function of concentration.

Multicellular pharmacodynamics

The concept of pharmacodynamics has been expanded to include *Multicellular Pharmacodynamics* (MCPD). MCPD is the study of the static and dynamic properties and relationships between a set of drugs and a dynamic and diverse multicellular 4 dimensional organization. It is the study of the workings of a drug on a minimal multicellular system (mMCS), both in vivo and in silico. *Networked Multicellular Pharmacodynamics* (Net-MCPD) further extends the concept of MCPD to model regulatory genomic networks together with signal transduction pathways, as part of a complex of interacting components in the cell. For a fuller explanation of these concepts see the articles:

- Jackson, R.C. (2003) Predictive software for drug design and development. Pharmaceutical Development and Regulation 1 ((3)), 159-168.
- Werner, E., In silico multicellular systems biology and minimal genomes, DDT vol 8, no 24, pp 1121-1127, Dec 2003. (Introduces the concepts MCPD and Net-MCPD)

A good source for further information and posting to experts can be found courtesy of Dr. David W. A. Bourne, OU College of Pharmacy

See also

- Pharmacokinetics
- Pharmaceutical company

Pharmaceutical industry

A *pharmaceutical company*, or *drug company*, is a company licensed to discover, develop, market and distribute drugs.

History

Most major pharmaceutical companies were founded in the late 19th and early 20th centuries, although it is only since the 1950's the industry got underway in earnest. The discovery of penicillin is widely regarded as the birth of modern pharmaceuticals - this was the moment where systematic scientific approaches, understanding of human biology and sophisticated manufacturing techniques all made the development of medicines possible. The industry remained relatively small scale until a long period of scientific advancements through the 1970s to present day elevated some companies to become among the most profitable and productive in the world.

The industry has delivered significantly improved treatment for patients and morbidity/ mortality rates across developing countries continue to fall due in no small part to the innovation of research-based pharmaceutical companies.

There are currently more than 200 major pharmaceutical companies. As in some other industries, economic pressures are forcing pharmaceutical companies toward greater efficiency. [1] The costs of research and manufacture of ever more sophisticated medicines

grows every year and the tension between the affordability of new medicines and their benefits look certain to be a continuing major debating point.

Biotechnology has offered new possibilities for the future. The first generation of 'biologic' therapies are already in use, especially in cancer. Vaccines, after many years in the research doldrums, are a renewed focus of interest as better understanding of genetics offers new ideas on how disease might be prevented. Looking to the far future it may even be possible, through the emerging science of pharmacogenomics, to tailor medicines to each individual.

Biotechnology company

A biotechnology company is any company that uses biological systems, living organisms, or derivatives thereof, to make or modify products or processes for specific use. Often biotechnology companies produce pharmaceuticals. Typically a biopharmaceutical made in this manner is composed of very large molecules that are unstable and must be administered by injection in a physician's office.

It remains a very exploratory area. Biotech companies very often start life as very small spin-offs from university research departments and are high-tech 'start-up' companies. They often need to get bought out or enter into a licensing agreement with a big mainstream pharmaceutical company to see their idea actually available for patients.

Drug discovery

Drug discovery is the process by which drugs are discovered and/or designed. In the past most drugs have been discovered either by identifying the active ingredient from traditional remedies or by serendipitous discovery. The new approach has been to understand how disease and infection are controlled at the molecular and physiology level and to target specific entities based on this knowledge. New technologies and Data Management/Informatics systems are now employed to speed up this process.

New drugs begin in the laboratory with chemists, scientists and pharmacologists who identify cellular and genetic factors that play a role in specific diseases. "They search for chemical and biological substances that target these biological markers and are likely to have drug-like effects. Out of every 5,000 new compounds identified during the discovery process, only five are considered safe for testing in human volunteers after preclinical evaluations. After three to six years of further clinical testing in patients, only one of these compounds is ultimately approved as a marketed drug for treatment. The following sequence of research activities begins the process that results in development of new medicines:"

Target identification

"Drugs usually act on either cellular or genetic chemicals in the body, known as targets, which are believed to be associated with disease. Scientists use a variety of techniques to identify and isolate a target and learn more about its functions and how these influence

disease. Compounds are then identified that have various interactions with drug targets helpful in treatment of a specific disease."

Target prioritization/validation

"To select targets most likely to be useful in the development of new treatments for disease, researchers analyze and compare each drug target to others based on their association with a specific disease and their ability to regulate biological and chemical compounds in the body. Tests are conducted to confirm that interactions with the drug target are associated with a desired change in the behavior of diseased cells. Research scientists can then identify compounds that have an effect on the target selected."

Lead identification

"A lead compound or substance is one that is believed to have potential to treat disease. Laboratory scientists can compare known substances with new compounds to determine their likelihood of success. Leads are sometimes developed as collections, or libraries, of individual molecules that possess properties needed in a new drug. Testing is then done on each of these molecules to confirm its effect on the drug target."

Lead optimization

"Lead optimization compares the properties of various lead compounds and provides information to help pharmaceutical and biotechnology companies select the compound or compounds with the greatest potential to be developed into safe and effective medicines. Often during this same stage of development, lead prioritization studies are conducted in living organisms (in vivo) and in cells in the test tube (in vitro) to compare various lead compounds and how they are metabolized and affect the body."

Drug development

Drug development is considered a costly and intensive process. Of all compounds investigated for use in humans only a small fraction is eventually approved, and only after heavy investment in pre-clinical development, clinical trials, and safety monitoring to determine the safety and efficacy of a compound. Most clinical trials are randomized and controlled. The cost for a new drug (new chemical entity) is estimated to be about 1 billion USD. This figure is however disputed:[3] Half of this amount are opportunity costs, others are costs for the development of all unsuccessful drugs. Apart from that: the author (di Masi) has never published details about his calculations or estimates. Depending on a number of considerations, a company may apply for and be granted a patent for the drug or the process of producing the drug for about 20 years. Only after rigorous study and testing, which can take as long as 12 years, will governmental authorities grant permission for the company to market and sell the drug. In special circumstances, such as the search for effective drugs to

treat AIDS, the Food and Drug Administration (FDA) has encouraged an abbreviated process for drug testing and approval called fast-tracking

Clinical testing is usually described as consisting of Phase I, Phase II and Phase III clinical studies In each successive phase, increasing numbers of patients are tested. There are a large number of firms worldwide that support clinical trials and perform clinical trials services for pharmaceutical firms.

Phase I Clinical Studies

"Phase I studies are designed to verify safety and tolerability of the candidate drug in humans and typically take six to nine months. These are the first studies conducted in humans. A small number of subjects, usually from 20 to 100 healthy volunteers, take the investigational drug for short periods of time. Testing includes observation and careful documentation of the pharmacodynamics and the pharmacokinetics of the drug - how the drug acts in the body, how it is absorbed, distributed, metabolized, excreted, its half-life etc."

Phase II Clinical Studies

"Phase II studies are designed to determine effectiveness and further study the safety of the candidate drug in humans. Depending upon the type of investigational drug and the condition it treats, this phase of development generally takes from six months up to three years. Testing is conducted with up to several hundred patients suffering from the condition the investigational drug is designed to treat. This testing determines safety and effectiveness of the drug in treating the condition and establishes the minimum and maximum effective dose. Most Phase II clinical trials are randomized, or randomly divided into groups, one of which receives the investigational drug, one of which gets a placebo containing no medication and sometimes a third that receives a current standard treatment to which the new investigational drug will be compared. In addition, most Phase II studies are double-blinded, meaning that neither patients nor researchers evaluating the compound know who is receiving the investigational drug or placebo."

Phase III Clinical Studies

"Phase III studies provide expanded testing of effectiveness and safety of an investigational drug, usually in randomized, and blinded clinical trials. Depending upon the type of drug candidate and the condition it treats, this phase usually requires one to four years of testing. In Phase III, safety and efficacy testing is conducted with several hundred to thousands of volunteer patients suffering from the condition the investigational drug treats."

New Drug Application

"(NDA)/Marketing Authorization Application (MAA) NDAs (in the U.S.) and MAAs (in the UK) are examples of applications to market a new drug. Such applications document safety and efficacy of the investigational drug and contain all the information collected during the

drug development process. At the conclusion of successful preclinical and clinical testing, this series of documents is submitted to the FDA in the U.S. or to the applicable regulatory authorities in other countries. The application must present substantial evidence that the drug will have the effect it is represented to have when people use it or under the conditions for which it is prescribed, recommended or suggested in the labeling. Obtaining approval to market a new drug frequently takes between six months and two years."

Orphan drug

There are special rules for certain rare diseases ("orphan diseases") involving fewer than 200,000 people in the United States. Because medical research and development of drugs to treat such diseases is financially disadvantageous, companies that do so are rewarded with tax reductions and a monopoly on that orphan drug for a limited time (seven years).

Post-approval surveillance

Some medications only show to have safety issues after they are marketed, as clinical trials are of a limited size, such as the 3,000 test subjects required by the FDA. Post-marketing surveillance ensures that after marketing the safety of a drug is monitored closely. In certain instances, its indication may need to be limited to particular patient groups, and in others the substance is withdrawn from the market completely.

After the FDA (or other regulatory agency for drugs marketed outside the U.S.) approves a new drug, pharmaceutical companies may conduct additional studies, including Phase IIIb and Phase IV studies.[6] "Late-stage drug development studies of approved, marketed drugs may continue for several months to several years."

Phase IIIb/IV Studies

"Phase IIIb trials, which often begin before approval, may supplement or complete earlier trials by providing additional safety data or they may test the approved drug for additional conditions for which it may prove useful. Phase IV studies expand testing of a proven drug to broader patient populations and compare the long-term effectiveness and/or cost of the drug to other marketed drugs available to treat the same condition."

Post-Market Studies

"Post-market studies test a marketed drug in new age groups or patient types. Some studies focus on previously unknown side effects or related risk factors. As with all stages of drug development testing, the purpose is to ensure the safety and effectiveness of marketed drugs."-side effects that are dangerous.

This activity is also often referred to as phase V and often entails the use of a large focus group.

Products

Drug information

Drug information and data are provided by the Food and Drug Administration (FDA) and are located at the Orange Book site. Drug information is commercially available at eKnowledgebase. Chemical structures and links to free information is also available on the web.

ICD and DRG

Diseases are classified by ICD-9 codes. These ICD codes are aggregated into approximately 500 diagnosis-related groupss (DRG) expected to have similar hospital use.

In 1991, the top 10 DRGs overall were:

- normal newborn,

vaginal delivery,
heart failure,
psychoses,
cesarean section,
neonate with significant problems,
angina pectoris,
specific cerebrovascular disorders,
pneumonia, and
hip/knee replacement.

These DRGs comprised nearly 30% of all hospital discharges.

Revenues

Industry revenues

2004 global dollar volume was $550 billion, a 7% increase over 2003—which in turn represented a 9% increase over 2002. US sales grew to $235.4 billion, a growth rate of 8.3% compared with 11.5% growth from 2002 to 2003. The United States accounts for 46% of the world's pharmaceutical market.

According to Teradata Magazine "By 2007, $40 billion in U.S. sales will be lost at the top 10 pharma companies as a result of the slowdown in R&D innovation and the expiry of patents on major products," ... "Taking a broader look across the industry, no fewer than 19 blockbuster drugs are expected to hit patent crisis by 2008. Analysis suggests that 150 mid-sized new compounds will be needed by 2007-2008 in the U.S. alone to plug this gap."

Top 10 pharmaceutical companies by sales

The top 10 pharmaceutical companies by 2004 sales are:

Rank	Company	Revenues (USD billions)	R&D Spend (USD billions)
1	Pfizer	50.9	7.5
2	GlaxoSmithKline	32.7	5.2
3	Sanofi-Aventis	27.1	3.9
4	Johnson & Johnson	24.6	5.2
5	Merck	23.9	4.0
6	Novartis	22.7	3.5
7	AstraZeneca	21.6	3.8
8	Hoffmann-La Roche	17.7	5.1
9	Bristol-Myers Squibb	15.5	2.5
10	Wyeth	14.2	2.5

Source: Wendy Diller and Herman Saftlas, "Healthcare: Pharmaceuticals," Standard & Poor's Industry Surveys, 22 December 2005, 13

Patents and Generics

Drugs are patentable. A typical patent lasts for 20 years. However, it often takes as long as 12 years to approve a drug for patient use. Patent protection allows the owner of the patent to charge high margins for the branded drug. When the patent for the drug runs out, a generic drug is usually created by a competing company and released, causing the price to drop markedly. Often the owner of the branded drug will introduce a generic version before the patent runs out in order to get a head start in the generic market.

Medicare Part D

In 2003 the United States enacted the Medicare Prescription Drug, Improvement, and Modernization Act (MMA), a program to provide prescription drug benefits to the elderly and disabled. This program is a component of Medicare (United States) and is known as "Medicare Part D." This program, set to begin in January 2006, will significantly alter the revenue models for pharmaceutical companies. Revenues from the program are expected to be $724 Billion between 2006 and 2015

Pharmaceuticals developed by biotechnological processes often must be injected in a physician's office rather than be delivered in the form of a capsule taken orally. Medicare payments for these drugs are usually made through Medicare Part B (physician office) rather than Part D (prescription drug plan).

Sales and marketing

The pharmaceutical industry is different

In most industries the purchaser, the payer and the user are the same person. The pharmaceutical industry is different from most industries in that the products are usually not chosen by the consumers or paid for by the consumers. Physicians control the choice of many drugs through prescription writing. Private insurance or public health bodies (e.g. the NHS in the UK) often pays for most of the drugs. Moreover, insurance companies and government health agencies restrict the drugs that can be prescribed through the use of formularies. This along with the high margins companies can realise for their most successful medicines make pharmaceutical marketing a complex discipline. There are a number of firms that specialize in data and analytics for pharmaceutical marketing

Advertising to physicians

Physicians are perhaps the most important players in pharmaceutical sales. They write the prescriptions that determine which drugs will be used by the patient. Influencing the physician is key to pharmaceutical sales. Historically, this was done with large pharmaceutical sales forces. A medium-sized pharmaceutical company might have a sales force of 1000 representaives. The largest companies have tens of thousands of representatives. Currently, there are approximately 100,000 pharmaceutical sales reps in the United States pursuing some 120,000 pharmaceutical prescribers. Drug companies spend $5 billion annually sending representatives to physician offices.

Direct to consumer

Since the 1980s new methods of marketing for prescription drugs to consumers have become important. Patients are far less deferential to doctors and will inquire about, or even demand, to receive a medication they have seen advertised on television. In the United States recent years have seen an increase in mass media advertisements for pharmaceuticals.

In almost all European countries, direct to consumer advertising is banned. This also reflects the more social health systems that operate that side of the Atlantic. US-style DTC advertising is hugely controversial in Europe and some of the excesses seen in the US have undoubtedly caused significant damage to the reputation of the industry.

The payers

Public and private insurers affect the writing of prescriptions by physicians through formularies that restrict the number and types of drugs that the insurer will cover. Not only can the insurer affect drug sales by including or excluding a particular drug from a formulary, they can affect sales by tiering, or placing bureaucratic hurdles to prescribing certain drugs. In January 2006, the U.S. instituted a new public prescription drug plan through its Medicare

program. Known as Medicare Part D, this program engages private insurers to negotiate with pharmaceutical companies for the placement of drugs on tiered formularies.

Regulation of Pharmaceutical Marketing and Distribution

The safety and effectiveness of prescription drugs in the U.S. is regulated by the federal Prescription Drug Marketing Act of 1987.

Mergers, acquisitions, and co-marketing of drugs

A merger, acquisition, or co-marketing deal between pharmaceutical companies can occur if the companies have complementary capabilities. A small biotechnology company might have a new drug but no sales or marketing capability. Conversely, a large pharmaceutical company might have unused capacity in a large sales force due to a gap in the company pipeline of new products. It may be in both company's interest to enter into a deal to capitalize on the synergy between the companies. The difference between the value of the two companies after the deal and before the deal is known as the synergy value of the deal.

Controversy

- Accusations of forging or suppressing clinical trial results to maximise sales of some medications.
- Accusations of manipulating the market for their products by excessive gifts to doctors
- Too much advertising materials in the doctor's office, such as clocks, poster ads, etc.
- Reluctance of the industry to fabricate treatments of diseases in less capable countries, such as malaria.
- Aggressive representation by pharmaceutical companies' salespeople (detailmen).
- Sponsorship of medical schools, with influence on the curriculum
- Increased number of drug tests on animals before FDA approval
- Criticism for the price of patented AIDS medication, which could limit therapeutic options for patients in the Third World, where the most people have AIDS. Under World Trade Organization rules, a developing country has options for obtaining needed medications under compulsory licensing or importation of cheaper versions of the drugs, even before patent expiration (WTO Press Release). Pharmaceutical companies often offer much needed medication at no or reduced cost to the developing countries. Proposals to allow the manufacture generic AIDS drugs are not without controversy; it is sometimes claimed that this might cause pharmaceutical companies to move away from AIDS drug research and focus their research on other, more profitable areas. In March of 2001, South Africa was sued by 41 pharmaceutical companies for their Medicines Act, which

allowed the import and generic production of cheap AIDS drugs. The case was later dropped after protest around the world.

- Between 1980 and 1997, drug industry funding for academic research rose eight fold, as research costs rose, and the rate of federal support fell. Drug researchers not employed by pharmaceutical companies often look to companies for grants, and companies often look to researchers for studies that will make their products look good. 79% of papers written by independent researchers are favorable to new drugs. 98% of papers written by researchers sponsored by the drug companies are favorable. Sponsored researchers are rewarded by drug companies by putting them on symposium circuits to lecture, with the lecture scripts written by pharmaceutical companies. Some researchers who have tried to publish papers that show harmful effects of new drugs or cheaper alternatives have been threatened by drug companies with lawsuits.
- Drug companies spent $900 million on consumer ads in the first half of 1999 alone. Pharmaceutical companies often fund non-profit "patient groups" that consume their drugs. Patient groups can advertise for the drug companies, and are unregulated by the FDA. Advertising directly to consumers, however, is strictly regulated in the United States by the FDA, as described in FDA Guidance for Industry on Consumer-Directed Broadcast Advertisements.
- Where pharmaceutics have been shown to cause side-effects, civil action has occurred, especially in countries where tort payouts are likely to be large. Due to high-profile cases leading to large compensations, most pharmaceutical companies endorse tort reform.
- According to the 2002 study "The price of innovation: new estimates of drug development costs" average out-of-pocket expenses for a single drug are US$ 403 million.

Pharmaceutical companies and the developing world

The role of pharmaceutical companies in the developing world is a matter of some debate, ranging from those arguing in favor of the billions of dollars of aid provided to the developing world to criticisms of the use of the poorest amongst us in human clinical trials, often without adequate protections, particularly in states lacking a strong rule of law.

In popular culture

Recent books and movies have been written in the west criticizing the western pharmaceutical companies role, or lack thereof, in healthcare in Africa. The most prominent of these is probably The Constant Gardener, a novel by John le Carré that was also turned into a movie.

Supporters of the plot of the movie arguing that it is realistic. However, detractors including staunch critics of the industry point out its flaws.

Tragedies in developing countries

An example of a tragedy is described in a Washington Post article from December 2000, in which a clinical trial conducted by a corrupt MD in Pfizer's name in Nigeria in 1996. That study allegedly used children to test Trovan, which had been proven efficacious in adults but not in children.

Charitable measures

There are innumerable charitable programs and drug discovery & development efforts undertaken by the industry without expectation of profit. Some prominent examples include:

- "Merck's Gift," wherein billions of free drugs were donated to cure River Blindness in Africa
- Pfizer's gift of free/discounted fluconazole and other drugs in AIDS-ravaged South Africa
- *GSK's development of a treatment for chloroquine-resistant malaria, despite the lack of profit potential* and their commitment to give free albendazole tablets to the WHO for, and until, the elimination of lymphatic filariasis worldwide.

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- Marcia Angell: The truth about the drug companies. Random House, New York, 2004, 305 S. ISBN 0-375-50846-5.

Industry Associations

- International Federation of Pharmaceutical Manufacturers and Associations (IFPMA)
European Federation of Pharmaceutical Industries and Associations (EFPIA)
Japan Pharmaceutical Manufacturers Association (JPMA)
Pharmaceutical Research and Manufacturers of America (PhRMA)

Regulatory authorities

- International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH)

European Medicines Agency (EMEA)
Food and Drug Administration (FDA)
Ministry of Health, Labour and Welfare (Japan)

See also

- Bioinformatics
- Biotechnology
- Drug design
- Drug discovery
- Medicine
- Orphan drug
- Pharmaceutical marketing
- Pharmacology

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Approved drug

In the United States, the FDA approves drugs. Before a drug can be prescribed, it must undergo an extensive FDA approval process. This process involves first testing the drug on animals or in medical labs. If found to be safe by the FDA and approved for the next phase of study, the drug is then tested for safety and effectiveness in humans (clinical trials). The drug manufacturer then files a New Drug Application to the FDA, which reviews the application and either approves or rejects it.

The U.S. and Canadian systems of new drug approvals are perhaps the most rigorous in the world. On average, it costs a company $359 million to get one new medicine from the laboratory to the pharmacist's shelf, according to a February 1993 report by the Congressional Office of Technology Assessment. It takes 12 years on average for an experimental drug to travel from lab to medicine chest. Only five in 5,000 compounds that enter preclinical testing make it to human testing. One of these five tested in people is approved.

See also

- Drug discovery
- Drug design
- Drug development
- Patent medicine
- Dietary supplement

Blockbuster drug

A *blockbuster drug* is a drug generating more than $1 billion of revenue for its owner each year. The search for blockbusters has been the foundation of the R&D strategy adopted by big pharmaceutical companies, but this looks set to change. New advances in genomics, and the promise of personalized medicine, are likely to fragment the pharmaceutical market.

A recent report from Urch Publishing estimated that about one third of the pharma market by value is accounted for by blockbusters. About 100 products are blockbusters. The top seller was Lipitor a cholesterol-lowering medication marketed by Pfizer with sales of US$12,187 million

Leading blockbuster drugs

- Atorvastatin (Lipitor) from Pfizer
- celecoxib (Celebrex) from Pfizer
- omeprazole (Losec/Prilosec) from AstraZeneca (2003 sales $2.6bn)
- esomeprazole (Nexium) from AstraZeneca (2003 sales $3.3bn)
- Fexofenadine (Telfast/Allegra) from Aventis (2004 sales $1.87bn)
- quetiapine (Seroquel) from AstraZeneca (2003 sales $1.5bn)
- metoprolol (Seloken/Toprol) from AstraZeneca (2003 sales $1.3bn)
- budesonide (Pulmicort/Rhinocort) from AstraZeneca (2003 sales $1.3bn, plus some fraction of the $0.6bn sales of Symbicort)

Further reading

Pharmaceutical Market Trends, 2006-2010, from Urch Publishing

Counterfeit drug

A *counterfeit drug* or a *counterfeit medicine* is a medication which is produced and sold with the intent to deceptively represent its origin, authenticity or effectiveness. The common street term for counterfeit drug is "beat bag." A counterfeit drug may be one which does not contain active ingredients, contains an insufficient quantity of active ingredients, or contains entirely incorrect active ingredients (which may or may not be harmful), and which is typically sold with inaccurate, incorrect, or fake packaging. Fake medicines and generic drugs which are deliberately mislabeled in order to deceive consumers are therefore counterfeit, while a drug which has not received regulatory approval is not necessarily so.

Overview

An individual who applies a counterfeit medication may experience a number of dangerous consequence to their health, such as unexpected side effects, allergic reactions, or a worsening of their medical condition. A number of counterfeits do not contain any active ingredients, and instead contain inert substances, which do not provide the patient any treatment benefits. Counterfeit medications may also contain incorrect ingredients, improper dosages of the correct ingredients, or they may contain hazardous ingredients.

The extent of the problem of counterfeit drugs is unknown. Counterfeiting is difficult to detect, investigate, and quantify. So, it is hard to know or even estimate the true extent of the problem. What is known is that they occur worldwide and are more prevalent in developing countries. It is estimated that upwards of 10% of drugs worldwide are counterfeit, and in some countries more than 50% of the drug supply is made up of counterfeit drugs. Furthermore, the World Health Organization estimates that the annual earnings of counterfeit drugs are over 32 Billion U.S. Dollars.

There are several technologies that may prove helpful in combating this problem, such as radio frequency identification, which uses electronic devices to track and identify items, such as pharmaceutical products, by assigning individual serial numbers to the containers holding each product. This technology may prevent the diversion or counterfeiting of drugs by allowing wholesalers and pharmacists to determine the identity and dosage of individual products. More recent innovative technology includes the use of mobile phone cameras to verify the source and authenticity of drugs within a world wide market through use of unique identifying unbreakable codes. video clip of mobile phone verification of authenticity of drugs

On May 6, 2005, the Chinese press agency Xinhua reported that the World Health Organization had established Rapid Alert System (RAS), the world's first web-based system for tracking the activities of drug cheats, in light of the increasing severity of the problem of counterfeit drugs.

Bacterial Resistance

Fake antibiotics with a low concentration of the active ingredients can do damage world wide. Courses of antibiotics that are not seen through to completion allow bacteria to regroup and develop resistance.

Television

A cable TV report featured a lady in Nigeria, Dr Dora, who was appointed to deal with fake drugs. According to these reports, many of the fake drugs came from the same countries that make normal drugs, especially China and India. In the case of India, while it is against the law to make fake drugs for internal use, it is not against the law to make fake drugs for export.

References

- New Scientist - September 9, 2006

Drug development

Drug Development or *Preclinical Development* is defined in many pharmaceutical companies as the process of taking a new chemical lead through the stages necessary to allow it to be tested in human clinical trials, although a broader definition would encompass the entire process of drug discovery and clinical testing of novel drug candidates.

New Chemical Entities (*NCEs*) are compounds which emerge from the process of drug discovery. These will have promising activity against a particular biological target thought to be important in disease, however little will be known about the safety, toxicity, pharmacokinetics and metabolism of this NCE in human. It is the function of drug development to assess all of these parameters prior to human clinical trials. A further major objective of drug development is to make a recommendation of the dose and schedule to be used the first time an NCE is used in a human clinical trial ("First-in-Man", FIM).

In addition, drug development is required to establish the physicochemical properties of the NCE: its chemical makeup, stability, solubility. The process by which the chemical is made will be optimized so that from being made at the bench on a milligram scale by a synthetic chemist, it can be manufactured on the kilogram and then on the ton scale. It will be further examined for its suitability to be made into capsules, tablets or intravenous formulations. Together these processes are known in preclinical development as *CMC*: Chemistry, Manufacturing and Control.

Many aspects of drug development are focused on satisfying the regulatory requirements of drug licensing authorities. These generally constitute a number of tests designed to determine the major toxicities of a novel compound prior to first use in man. It is a legal requirement that an assessment of major organ toxicity be performed (effects on the heart and lungs, brain, kidney, liver and digestive system), as well as effects on other parts of the body that might be affected by the drug (e.g. the skin if the new drug is to be delivered through the skin). While, increasingly, these tests can be made using in vitro methods (e.g. with isolated cells), many tests can only be made by using experimental animals, since it is only in an intact organism that the complex interplay of metabolism and drug exposure on toxicity can be examined.

The process of drug development does not stop once an NCE begins human clinical trials. In addition to the tests required to move a novel drug into the clinic for the first time it is also important to ensure that long-term or chronic toxicities are determined, as well as effects on systems not previously monitored (fertility, reproduction, immune system, etc). The compound will also be tested for its ability to cause cancer (carcinogenicity testing).

If a compound emerges from these tests with an acceptable toxicity and safety profile, and it can further be demonstrated to have the desired effect in clinical trials, then it can be submitted for marketing approval in the various countries where it will be sold. In the US,

this process is called a New Drug Application or NDA. Most NCEs, however, will fail during drug development, either because they have some unacceptable toxicity, or because they simply do not work in clinical trials.

See also

- Drug design
- Drug discovery
- Pharmaceutical company

Generic drug

A *generic drug* (pl. generic drugs, short: generics) is a drug which is bioequivalent to a brand name drug with respect to pharmacokinetic and pharmacodynamic properties. These drugs are usually sold at a lower price than the brand name drug. Generic medicines must contain the same active ingredient at the same strength as the "innovator" brand, be bioequivalent, and are required to meet the same pharmacopoeial requirements for the preparation. By extension, therefore, generics are assumed to be identical in dose, strength, route of administration, safety, efficacy, and intended use.

Reasons for cheaper price

The principal reason for the reduced price of generic medicines is that these companies incur less costs in creating the generic drug and are therefore able to offer a lower price and still maintain profitability.

Manufacturers of generic drugs are mainly able to avoid the following three costs that brand name pharmaceutical companies incur: (1) costs associated with the research and development of the drug; (2) costs associated with the navigating governmental bureaucracy for getting a drug onto the market as safe and effective; and (3) marketing costs.

First, Generic manufacturers do not have to incur the costs of searching and finding a new drug to treat an illness because they have access to adequate information regarding the brand name drug to allow them to manufacture a bioequivalent version of the brand name drug that will do the same thing.

Second, generic manufacturers do not have to prove that their product is safe and effective through clinical trials, only that their drug is bioequivalent.

Third, these companies receive the large benefit of the marketing that goes into pushing the innovator drug. The drugs that generic manufacturers are selling have been on the market for usually a decade or more and do not need additional advertising. For the same reason, generic manufacturers also do not give away sample doses to promote their products. The significant research and development and marketing costs incurred by the large pharmaceutical companies in bringing a new drug to the market is often cited as the

reason for the high cost of new agents - they wish to recover these costs before the patent expires. Generic manufacturers do not incur these costs, with bioequivalence testing and the actual manufacturing process costing relatively little, and are able to charge significantly less than the "innovator" brand.

When can a generic drug be produced

Generic drugs can be legally produced for drugs where: 1) the patent has expired, 2) the generic company certifies the brand company's patents are either invalid, unenforceable or will not be infringed, 3) for drugs which have never held patents, or 4) in countries where a patent(s) is/are not in force. The expiration of a patent removes the monopoly of the patent holder on drug sales licensing. It is also becoming popular for the large pharmaceutical companies to preempt the expiry of their patent by producing their own generic product, or license their own product to be branded by generic companies. Thus, in some cases, the "generic" product is actually the brand product but inside a different box.

Enacted in 1984, the U.S. Drug Price Competition and Patent Term Restoration Act, informally known as the "Hatch-Waxman Act", standardized U.S. procedures for recognition of generic drugs. An applicant files an Abbreviated New Drug Application (or "ANDA") with the Food and Drug Administration (FDA) and seeks to demonstrate therapeutic equivalence to a specified, previously approved "reference listed drug." When an ANDA is approved, the FDA adds the drug to its Approved Drug Products list, also known as the "Orange Book", and annotates the list to show equivalence between the reference listed drug and the approved generic. The FDA also recognizes drugs using the same ingredients with different bioavailability and divides them into therapeutic equivalence groups. For example, as of 2006 diltiazem hydrochloride had four equivalence groups all using the same active ingredient but considered equivalent only within a group. For an explanation of FDA terms and procedures, see "Approved Drug Products with Therapeutic Equivalence Evaluations, Preface."

Patent lifetime and research cost issues

Pharmaceutical companies may produce a generic drug when the patent expires on the innovator drug. Patent lifetime differs from country to country. The length of time before a patent expires varies for different drugs. Usually, there is no way to renew a patent after it expires. A new version of the drug with significant changes to the compound could be patented but this will require new clinical trials and will not prevent the generic versions of the original drug. Usually, generic drugs are much less expensive than the brand-name product. Some patients and physicians will hesitate to select these medications because of concerns about the quality of generic drugs. When a pharmaceutical company first markets a drug, it is usually under a patent that allows only the pharmaceutical company that developed the drug to sell it. This allows the company to recoup the cost of developing that particular drug. It costs on average around $800,000,000 to develop and test a new drug before it is approved for use. After the patent on a drug expires, any pharmaceutical company can manufacture and sell that drug. Since the drug has already been tested and approved, the cost of simply manufacturing the drug will be a fraction of the original cost of testing and

developing that particular drug. The brand-name drug companies have tended to litigate aggressively to extend patent protection on their medicines and keep generic versions off the market, a process referred to by critics as "evergreening."

Ensuring bioequivalence

In the USA the Food and Drug Administration (FDA) is responsible for making sure that generic drugs are "safe and effective." The approval process for generic drugs began in the late 1960s. Generic drug manufacturers were required to prove that their formulation exhibits bioequivalence to the innovator product. Over the past several years there have been studies that have shown the effectivness and safety of some generic drugs. Generic drugs are always less expensive and can save patients and insurance companies thousands of dollars supposedly without compromising the quality of care. The FDA must approve generic drugs just as innovator drugs must be approved. Bioequivalence, however, does not mean that generic drugs are exactly the same as their innovator product counterparts, as chemical differences do exist. Some doctors and patients emphatically believe that certain generic drugs are not as effective as the products they are meant to replace (ie. Prozac, Oxycontin), and consumers would undoubtedly benefit from more clinical studies done on drug by drug basis.

180 Day Generic Drug Exclusivity

The US FDA offers a 180 day exclusivity period to generic drug manufacturers in specific cases. During this period only one (or sometimes a few) generic manufacturers can produce the generic version of a drug. This exclusivity period is only used when a generic manufacturer argues that a patent is invalid or is not violated in the generic production of a drug, and the period acts as a reward for the generic manufacturer who is willing to risk liability in court and the cost of patent court litigation. There is often contention around these 180 day exclusivity periods because a generic producer does not have to produce the drug during this period and can file an application first to prevent other generic producers from selling the drug.

Large pharmaceutical companies often spend thousands of dollars protecting their patents from generic competition. Apart from litigation, companies use other methods such as reformulation or licensing a subsidiary (or another company) to sell generics under the original patent. Generics sold under license from the patent holder are known as *authorized generics*; they are not affected by the 180 day exclusivity period as they fall under the patent holder's original drug application.

A prime example of how this works is simvastatin (Zocor), a popular drug created and manufactured by U.S. based pharmaceutical Merck & Co., which lost its US patent protection on June 23, 2006. India-based Ranbaxy Laboratories (at the 80-mg strength) and Israel-based Teva Pharmaceutical Industries (at all other strengths) received 180 day exclusivity periods for simvastatin; due to Zocor's popularity, both companies began marketing their products immediately after the patent expired. However, Dr. Reddy's Laboratories also markets an authorized generic version of simvastatin under license from Zocor's

manufacturer, Merck & Co.; some packages of Dr. Reddy's simvastatin even show Merck as the actual manufacturer and have Merck's logo on the bottom.

Further reading

Fighting generic competition: strategies for research-based companies, Urch Publishing

Pharmaceutical marketing

Pharmaceutical marketing is the business of advertising or otherwise promoting the sale of pharmaceuticals or drugs.

History

The marketing of medication has a long history. The sale of miracle cures, many with little real potency, has always been common. Marketing of legitimate non-prescription medications, such as pain relievers or allergy medicine, has also long been practiced. Mass marketing of prescription medications was rare until recently, however. It was long believed that since doctors made the selection of drugs, mass marketing was a waste of resources; specific ads targeting the medical profession were thought to be cheaper and just as effective. This would involve ads in professional journals and visits by sales staff to doctor’s offices and hospitals. An important part of these efforts was marketing to medical students.

Direct and indirect marketing to health care providers

Physicians are perhaps the most important players in pharmaceutical sales. They write the prescriptions that determine which drugs will be used by the patient. Influencing the physician is the key to pharmaceutical sales. Historically, this was done by a large pharmaceutical sales force. A medium-sized pharmaceutical company might have a sales force of 1000 representatives. The largest companies have tens of thousands of representatives. Sales representatives called upon physicians regularly, providing information and free drug samples to the physicians. This is still the approach today; however, economic pressures on the industry are causing pharmaceutical companies to rethink the traditional sales process to physicians.

Pharmaceutical companies are developing processes to influence the people who influence the physicians. There are several channels by which a physician may be influenced, including self-influence through research, peer influence, direct interaction with pharmaceutical companies, patients, and public or private insurance companies.

There are a number of firms that specialize in data and analytics for pharmaceutical marketing

Individual research

Physicians discover pharmaceutical information from such sources as the Physician's Desk Reference and online sources, as well as via PDAs with applications.

They also rely upon pharmaceutical-branded e-detailing sites, pharmaceutical sales and non-sales representatives, and scholarly literature. Scholarly literature can be in the form of medical journal article reprints, often delivered by sales representatives at their place of employment or at conference exhibitions.

Journal article reprints are available from companies.

Peer influence

- Key opinion leaders

Key opinion leaders (KOL), or "thought leaders", are respected individuals, such as prominent medical school faculty, who influence physicians through their professional status. Pharmaceutical companies generally engage key opinion leaders early in the drug development process to provide advocacy and key marketing feedback Some pharmaceutical companies identify key opinion leaders through direct inquiry of physicians (primary research).

- Colleagues

Physicians acquire information through informal contacts with their colleagues, including social events, professional affiliations, common hospital affiliations, and common medical school affiliations. Some pharmaceutical companies identify influential colleagues through commercially available prescription writing and patient level data (see list of data providers in this article).

Direct contact with pharmaceutical sales representatives

Currently, there are approximately 100,000 pharmaceutical sales reps in the United States pursuing some 200,000 pharmaceutical prescribers. A pharmaceutical representative will often try to see a given physician every few weeks. Representatives often have a call list of about 200 physicians with 120 targets that should be visited in 4-6 week cycles.

Because of the large size of the pharmaceutical sales force, the organization, management, and measurement of effectiveness of the sales force are significant business challenges. Management tasks are usually broken down into the areas of physician targeting, sales force size and structure, sales force optimization, call planning, and sales forces effectiveness.

Physician targeting

Marketers attempt to identify the universe of physicians most likely to prescribe a given drug. Historically, this was done by measuring the number of total prescriptions (TRx) and new prescriptions (NRx) per week that each physician writes. This information is collected by commercial vendors (see list in this article). The physicians are then "deciled" into ten

groups based on their writing patterns. Higher deciles are more aggressively targeted. Some pharmaceutical companies use additional information such as:

- profitability of a prescription (script),
- accessibility of the physician,
- tendency of the physician to use the pharmaceutical company's drugs,
- effect of managed care formularies on the ability of the physician to prescribe a drug,
- the adoption sequence of the physician (that is, how readily the physician adopts new drugs in place of older, established treatments), and
- the tendency of the physician to use a wide palette of drugs
- influence that physicians have on their colleagues.

Data for drugs prescribed in a hospital are not usually available at the physician level. Advanced analytic techniques are used to value physicians in a hospital setting.

Sales force size and structure

Marketers must decide on the appropriate size of a sales force needed to sell a particular portfolio of drugs to the target universe. Design the optimal reach (how many physicians to see) and frequency (how often to see them) for each individual physician. Decide how many sales representatives to devote to office and group practice and how many to devote to hospital accounts.

Patients

Since the 1980s, new methods of marketing prescription drugs to consumers have become important. Patients are far less deferential to doctors and will inquire about, or even demand to receive, a medication they have seen advertised on television. In the United States, recent years have seen an increase in mass media advertisements for pharmaceuticals. Expenditures on direct-to-consumer (DTC pharmaceutical advertising) have more than quintupled in the last seven years since the FDA changed the guidelines, from $700 million in 1997 to more than $4 billion in 2004.

Private and public insurers

Public and private insurers affect the writing of prescriptions by physicians through formularies that restrict the number and types of drugs that the insurer will cover. Not only can the insurer affect drug sales by including or excluding a particular drug from a formulary, they can affect sales by tiering, or placing bureaucratic hurdles to prescribing certain drugs. In January 2006, the U.S. instituted a new public prescription drug plan through its Medicare program. Known as Medicare Part D, this program engages private insurers to negotiate with pharmaceutical companies for the placement of drugs on tiered formularies.

Regulation

In the United States, marketing and distribution of pharmaceuticals is regulated by the federal Prescription Drug Marketing Act of 1987.

Controversy

- The mass marketing to consumers of pharmaceuticals is controversial. It is banned in every western country except the US and New Zealand, which is considering a ban. Some feel it is better to leave the decision wholly in the hands of medical professionals; others feel that consumer education and participation in health is useful, but consumers need independent, comparative information about drugs (not promotional information)[4]. For these reasons, most countries impose limits on pharmaceutical mass marketing that are not placed on the marketing of other products. In some areas it is required that ads for drugs include a list of possible side effects, so that consumers are informed of both facets of a medicine. Canada's limitations on pharmaceutical advertising ensure that commercials that mention the name of a product cannot in any way describe what it does. Commercials that mention a medical problem cannot also mention the name of the product for sale; at most, they can direct the viewer to a website or telephone number operated by the pharmaceutical company.
- The number and persistence of pharmaceutical representatives has placed a burden on the time of physicians. "As the number of reps went up, the amount of time an average rep spent with doctors went down—so far down, that tactical scaling has spawned a strategic crisis. Physicians no longer spend much time with sales reps, nor do they see this as a serious problem."
- Recent legal cases and US congressional hearings have provided access to pharmaceutical industry documents revealing new marketing strategies for drugs. Activities once considered independent of promotional intent, including continuing medical education and medical research, are used, including paying to publish articles about promoted drugs for the medical literature, and alleged suppression of unfavorable study results.

See also

- Pharmaceutical company
- Pharmacology
- Biotechnology

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Standard treatment

Standard treatment (Active Control). The treatment that is normally provided to people with a given condition. In many studies, a control group receives the standard treatment while a treatment group receives the experimental treatment. After the clinical trial, researchers compare the outcomes of the two groups to see if the experimental treatment is better than, as good as or not as beneficial as the standard treatment.

Active (Positive) Concurrent Control

In an active control (or positive control) trial, subjects are randomly assigned to the test treatment or to an active control treatment. Such clinical trial s are usually double-blind, but this is not always possible; many oncology trials, for example, are considered difficult or impossible to blind because of different regimens, different routes of administration, and different toxicities. Active control trials can have two distinct objectives with respect to showing efficacy: (1) to show efficacy of the test treatment by showing it is as good as a known effective treatment or (2) to show efficacy by showing superiority of the test treatment to the active control. They may also be used with the primary objective of comparing the efficacy and/or safety of the two treatments . Whether the purpose of the trial is to show efficacy of the new treatment or to compare two treatments, the question of whether the trial would be capable of distinguishing effective from less effective or ineffective treatments is critical .

See also

- Drug development

Pharmacy

Pharmacy (from the Greek Æ¬Á¼±º¿½ = drug) is a transitional field between health sciences and chemical sciences and a profession charged with ensuring the safe use of medication. Traditionally, pharmacists have compounded and dispensed medications on the orders of physicians. More recently, pharmacy has come to include other services related to patient care including clinical practice, medication review, and drug information. Some of these new pharmaceutical roles are now mandated by law in various legislatures. Pharmacists, therefore, are drug therapy experts, and the primary health professionals who optimise medication management to produce positive health-outcomes.

The symbols most commonly associated with pharmacy are the mortar and pestle and the (recipere) character. Pharmacy organisations often employ other elements, such as the Bowl of Hygieia, conical measures, and caduceuses in their logos. Other symbols are common in different countries such as the green Greek cross in France and Great Britain, the increasingly-rare Gaper in The Netherlands, and a red stylised letter A in Germany and Austria, Apotheke being the German word for pharmacy.

Disciplines

The field of Pharmacy can generally be divided into three main disciplines:

- Pharmaceutics
- Pharmaceutical chemistry **and Pharmacognosy**
- Pharmacy practice

The boundaries between these disciplines and with other sciences, such as biochemistry, are not always clear-cut; and often, collaborative teams from various disciplines research together.

Pharmacology is sometimes considered a fourth discipline of pharmacy. Although pharmacology is essential to the study of pharmacy, it is not specific to pharmacy. Therefore it is usually considered to be a field of the broader sciences.

There are various specialties of pharmacy practice. Some specialisation is based on the place of practice including: community, hospital, consultant, locum, drug information, regulatory affairs, industry, and academia. Other specialisations are based on clinical roles including: nuclear, oncology, cardiovascular, infectious disease, diabetes, nutrition, geriatric, and psychiatric pharmacy.

Pharmacists

Main article: Pharmacist

Pharmacists are highly-trained and skilled healthcare professionals who perform various roles to ensure optimal health outcomes for their patients. Many pharmacists are also small-business owners, owning the pharmacy in which they practice. This unique dichotomy is often the subject of debate within the profession—in part due to the perception of pharmacists as "common shopkeepers" by many in the community.

Pharmacists are represented internationally by the International Pharmaceutical Federation (FIP). They are represented at the national level by professional organisations such as the Royal Pharmaceutical Society of Great Britain (RPSGB), the Pharmaceutical Society of Australia (PSA), the American Pharmacists Association (APhA), and the American Society of Health-System Pharmacists (ASHP).

In some cases, the representative body is also the registering body, which is responsible for the ethics of the profession. Since the Shipman Inquiry, there has been a move in the UK to separate the two roles.

Separation of prescribing from dispensing

In most jurisdictions (such as the United States), pharmacists are regulated separately from physicians. Specifically, the legislation stipulates that the practice of prescribing must be separate from the practice of dispensing. These jurisdictions also usually specify that only pharmacists may supply scheduled pharmaceuticals to the public, and that pharmacists cannot form business partnerships with physicians or give them "kickback" payments. However, the American Medical Association (AMA) Code of Ethics provides that physicians may dispense drugs within their office practices as long as there is no patient exploitation and patients have the right to a written prescription that can be filled elsewhere. 7 to 10 percent of American physician practices reportedly dispense drugs on their own.[1]

In other jurisdictions (particularly in Asian countries such as China, Hong Kong, Malaysia, and Singapore), doctors are allowed to dispense drugs themselves and the practice of pharmacy is sometimes integrated with that of the physician, particularly in traditional Chinese medicine.

In Canada it is common for a medical clinic and a pharmacy to be located together and for the ownership in both enterprises to be common, but licensed separately.

The reason for the majority rule is the high risk of a conflict of interest. Otherwise, the physician has a financial self-interest in "diagnosing" as many conditions as possible, and in exaggerating their seriousness, because he or she can then sell more medications to the patient. Such self-interest directly conflicts with the patient's interest in obtaining cost-effective medication and avoiding the unnecessary use of medication that may have side-effects.

A campaign for separation has begun in many countries and has already been successful (like in Korea). As many of the remaining nations move towards separation, resistance and lobbying from dispensing doctors who have pecuniary interests may prove a major stumbling block (e.g. in Malaysia).

Community pharmacy

A *pharmacy* (commonly the *chemist* in Australia, New Zealand and the UK; or *drugstore* in North America; or Apothecary, historically) is the place where most pharmacists practise the profession of pharmacy. It is the community pharmacy where the dichotomy of the profession exists—health professionals who are also retailers.

Community pharmacies usually consist of a retail storefront with a dispensary where medications are stored and dispensed. The dispensary is subject to pharmacy legislation;

with requirements for storage conditions, compulsory texts, equipment, etc., specified in legislation. Where it was once the case that pharmacists stayed within the dispensary compounding/dispensing medications; there has been an increasing trend towards the use of trained pharmacy technicians while the pharmacist spends more time communicating with patients.

All pharmacies are required to have a pharmacist on-duty at all times when open. In many jurisdictions, it is also a requirement that the owner of a pharmacy must be a registered pharmacist (R.Ph.). This latter requirement has been revoked in many jurisdictions, such that many retailers (including grocery stores and mass merchandisers) now include a pharmacy as a department of their store.

Likewise, many pharmacies are now rather grocery store-like in their design. In addition to medicines and prescriptions, many now sell a diverse arrange of additional household items such as shampoo, bandages, office supplies, candy, and snack foods.

Hospital pharmacy

Pharmacies within hospitals differ considerably from community pharmacies. Some pharmacists in hospital pharmacies may have more complex clinical medication management issues whereas pharmacists in community pharmacies often have more complex business and customer relations issues. Because of the complexity of medications including specific indications, effectiveness of treatment regimens, safety of medications (i.e., drug interactions) and patient compliance issues (in the hospital and at home) many pharmacists practising in hospitals gain more education and training after pharmacy school through a pharmacy practice residency and sometimes followed by another residency in a specific area. Those pharmacists are often referred to as clinical pharmacists and they often specialize in various disciplines of pharmacy. For example, there are pharmacists who specialize in haematology/oncology, HIV/AIDS, infectious disease, critical care, emergency medicine, toxicology, nuclear pharmacy, pain management, psychiatry, anticoagulation clinics, herbal medicine, neurology/epilepsy management, paediatrics, neonatal pharmacists and more.

Hospital pharmacies can usually be found within the premises of the hospital. Hospital pharmacies usually stock a larger range of medications, including more specialized medications, than would be feasible in the community setting. Most hospital medications are unit-dose, or a single dose of medicine. Hospital pharmacists and trained pharmacy technicians compound sterile products for patients including total parenteral nutrition (TPN), and other medications given intravenously. This is a complex process that requires adequate training of personnel, quality assurance of products, and adequate facilities. Some hospital pharmacies have decided to outsource high risk preparations and some other compounding functions to companies who specialize in compounding.

Consultant pharmacy

Consultant pharmacy practice focuses more on medication regimen review (i.e. "cognitive services") than on actual dispensing of drugs. Consultant pharmacists most typically work in nursing homes, but are increasingly branching into other institutions and

non-institutional settings. Traditionally consultant pharmacists were usually independent business owners, though in the United States many now work for several large pharmacy management companies (primarily Omnicare, Kindred Healthcare, and PharMerica[2]). This trend may be gradually reversing as consultant pharmacists begin to work directly with patients, primarily because many elderly people are now taking numerous medications but continue to live outside of institutional settings. Some community pharmacies employ consultant pharmacists and/or provide consulting services.

Internet pharmacy

Since about the year 2000, a growing number of Internet pharmacies have been established worldwide. Many of these pharmacies are similar to community pharmacies, and in fact, many of them are actually operated by brick-and-mortar community pharmacies that serve consumers online and those that walk in their door. The primary difference is the method by which the medications are requested and received. Some customers consider this to be more convenient and private method rather than traveling to a community drugstore where another customer might overhear about the drugs that they take. Internet pharmacies (also known as Online Pharmacies) are also recommended to some patients by their physicians if they are homebound.

While most Internet pharmacies sell prescription drugs and require a valid prescription, some Internet pharmacies sell prescription drugs without requiring a prescription. Many customers order drugs from such pharmacies to avoid the "inconvenience" of visiting a doctor or to obtain medications which their doctors were unwilling to prescribe. However, this practice has been criticized as potentially dangerous, especially by those who feel that only doctors can reliably assess contraindications, risk/benefit ratios, and an individual's overall suitability for use of a medication. There also have been reports of such pharmacies dispensing substandard products. Of course as history has shown, substandard products can be dispensed by both Internet and Community pharmacies, so it is best that the buyer beware.

Canada is home to dozens of licensed Internet pharmacies, many which sell their lower-cost prescription drugs to U.S. consumers, who pay the world's highest drug prices. However, there are Internet pharmacies in many other countries including Israel, Fiji and the UK that serve customers worldwide.

In the United States, there has been a push to legalize importation of medications from Canada and other countries, in order to reduce consumer costs. While in most cases importation of prescription medications violates Food and Drug Administration (FDA) regulations and federal laws, enforcement is generally targeted at international drug suppliers, rather than consumers. There is no known case of any U.S. citizens buying Canadian drugs for personal use with a prescription, who has ever been charged by authorities.

The future of pharmacy

In the coming decades, pharmacists are expected to become more integral within the health care system. Rather than simply dispensing medication, pharmacists expect to be paid for their cognitive skills.[3]

This paradigm shift has already commenced in some countries; for instance, pharmacists in Australia receive remuneration from the Australian Government for conducting comprehensive Home Medicines Reviews. In Great Britain, pharmacists (and nurses) who undertake additional training are obtaining prescribing rights. In the United States, consultant pharmacists, who traditionally operated primarily in nursing homes are now expanding into direct consultation with patients, under the banner of "senior care pharmacy."[4]

Many universities are altering their programs to increase emphasis in fields such as pharmacotherapeutics, clinical pharmacy, nuclear pharmacy, disease state management, etc.

See also

- Pharmaceutical company
-

Adverse drug reaction

An *adverse drug reaction* (abbreviated *ADR*) is a term to describe the unwanted, negative consequences sometimes associated with the use of medications. ADR is a particular type of adverse effect. The term is preferred over the colloquial and imprecise "side effect", as the term "side effect" implies the potential for beneficial consequences and that the effects are not explained by the pharmacological actions of the drug. The focused study of ADRs is the concern of the field known as *pharmacovigilance*

While ADR is probably the most precise term to describe the concept, it is not widely used in the community since it may be perceived as jargon and because of the negative-associations with the term "drug". Alternative terms with equivalent meaning to ADR include: *side effect*, adverse event, adverse effect, etc.

There are many types of ADRs:

- Type A, pharmacologically predictable
- Type B, bizarre and unpredictable
- Type C, arising from chronic use
- Type D, delayed reaction
- Type E, end of dose reaction
- Type F, Failure of therapy

Why do Adverse Drug Reactions (ADRs) matter and how do they happen?

ADRs matter because pharmaceutical products and other substances taken for medical purposes have the potential for harming patients, even killing them. ADRs happen for many reasons, some inevitable and unavoidable, some preventable.

The inevitable reasons are:

- The effects of any medical intervention cannot be predicted with absolute certainty
- There is no drug or medical intervention which will not have some negative and undesirable effect on someone, somewhere at some time
- Information about rare events may, by their very nature, not be available until they happen.

The preventable reasons include:

- An error in diagnosing the disease
- Prescription of the wrong drug for the disease
- Prescription of the wrong dose of the right drug
- Choice of the right drug for the disease, but maybe the wrong drug for the patient, because of some genetic or ethnic predisposition, age, some other illness or medication, some allergy or intolerance
- Choice of an appropriate drug but without taking into account potentially harmful interactive effects with other drugs or substances being taken
- In relation to all the above, the full indications, contraindications and risks of the drug may not have been read or fully understood
- The patient may not comply with the doctor's advice or manufacturer's advice in the patient information leaflet
- People choosing drugs and other substances for their own medication may cause problems.

The remedies for these hugely challenging problems:'

- A higher priority in medical training in taking case-histories, diagnostic skills, pharmacology, and the recognition and reporting of adverse effects
- Greater awareness by healthcare professionals and the public about the complexities and benefit-harm-risk profiles of medical interventions
- More effective communication and openness about the nature of drugs and their effects and the degree of uncertainty associated with them
- Public education and debate about the benefits, harm and risks of medical interventions and agreement about the balance of benefit, harm and risk which is acceptable, given that there will always be some uncertainty.
- Wider discussion and education in the nature of risk in general and its communication, and in the individual variables affecting perception and acceptance of risk.

Regulatory authorities and guidelines

Monitoring of ADRs is highly regulated and is being monitored by regulatory authorities during clinical trials and after a new drug is on the market:

- European Medicines Agency (EMEA)

Food and Drug Administration (FDA)
Ministry of Health, Labour and Welfare (Japan)
Uppsala Monitoring Centre (WHO)
CIOMS Guidelines
Pharmacovigilance
EudraVigilance (European Union)
Yellow Card Scheme (UK)

See also

- Adverse effect (medicine) *parent concept*
- Medical prescription

Chinese herbology

Herbology is the Chinese art of combining medicinal herbs.

Herbology is traditionally one of the more important modalities utilized in traditional Chinese medicine (TCM). Each herbal medicine prescription is a cocktail of many herbs tailored to the individual patient. One batch of herbs is typically decocted twice over the course of one hour. The practitioner usually designs a remedy using one or two main ingredients that target the illness. Then the practitioner adds many other ingredients to adjust the formula to the patient's yin/yang conditions. Sometimes, ingredients are needed to cancel out toxicity or side-effects of the main ingredients. Some herbs require the use of other ingredients as catalyst or else the brew is ineffective. The latter steps require great experience and knowledge, and make the difference between a good Chinese herbal doctor and an amateur. Unlike western medications, the balance and interaction of all the ingredients are considered more important than the effect of individual ingredients. A key to success in TCM is the treatment of each patient as an individual.

Chinese herbology often incorporates ingredients from all parts of plants, the leaf, stem, flower, root, and also ingredients from animals and minerals. The use of parts of endangered species (such as seahorses, rhinoceros horns, and tiger bones) has created controversy and resulted in a black market of poachers who hunt restricted animals. Many herbal manufacturers have discontinued the use of any parts from endangered animals.

History of Chinese herbology

Chinese herbs have been used for centuries. The first herbalist in Chinese tradition is Shennong, a mythical personage, who is said to have tasted hundreds of herbs and imparted

his knowledge of medicinal and poisonous plants to the agricultural people. The first Chinese manual on pharmacology, the Shennong Bencao Jing (Shennong Emperor's Classic of Materia Medica), lists some 365 medicines of which 252 of them are herbs, and dates back somewhere in the 1st century C.E. Han dynasty. Earlier literature included lists of prescriptions for specific ailments, exemplified by a manuscript "Recipes for 52 Ailments", found in the MaWangDui tomb, sealed in 168 B.C.E.

Succeeding generations augmented on this work, as in the Yaoxing Lun (o'º; also spelled Yao Xing Lun; literally "Treatise on the Nature of Medicinal Herbs"), a 7th century Tang Dynasty Chinese treatise on herbal medicine.

Arguably the most important of these was the Compendium of Materia Medica (Bencao Gangmu) compiled during the Ming dynasty by Li Shizhen, which is still used today for consultation and reference.

The history of this literature is presented in Paul U. Unschuld's "Medicine in China: a History of Pharmaceutics"; Univ. of Calif. Press, 1986.

Categorizing Chinese herbs

Chinese physicians used several different methods to classify traditional Chinese herbs:

- The Four Natures
- The Five Tastes
- The Meridians

The earlier (Han through Tang eras) Ben Cao (Materia Medicae) began with a three-level categorization:

Low level -- drastic acting, toxic substances Middle level -- medicinal physiological effects High level -- health and spirit enhancement

During the neo-Confucian Song-Jin-Yuan era (10th to 12th Centuries), the theoratical framework from acupuncture theory (which was rooted in Confucian Han theory) was formally applied to herbal categorization (which was earlier more the domain of Daoist natural science). In particular, alignment with the Five Phases (Tastes) and the 12 channels (Meridians theory) came to be used after this period.

The Four Natures

This pertains to the degree of yin and yang, ranging from cold (extreme yin), cool, neutral to warm and hot (extreme yang). The patient's internal balance of yin and yang is taken into account when the herbs are selected. For example, medicinal herbs of "hot", yang nature are used when the person is suffering from internal cold that requires to be purged, or when the patient has a general cold constituency. Sometimes an ingredient is added to offset the extreme effect of one herb.

The Five Tastes

The five tastes are pungent, sweet, sour, bitter and salty, each of which their functions and characteristics. For example, pungent herbs are used to generate sweat and to direct and

vitalize qi and the blood. Sweet-tasting herbs often tonify or harmonize bodily systems. Some sweet-tasting herbs also exhibit a bland taste, which helps drain dampness through diuresis. Sour taste most often is astringent or consolidates, while bitter taste dispels heat, purges the bowels and get rid of dampness by drying them out. Salty tastes soften hard masses as well as purge and open the bowels.

The Meridians

The Meridians refer to which organs the herb acts upon. For example, menthol is pungent, cool and is linked with the lungs and the liver. Since the lungs is the organ which protects the body from invasion from cold and influenza, menthol can help purge coldness in the lungs and invading heat toxins caused by hot "wind".

50 fundamental herbs

In Chinese herbology, there are 50 "fundamental herbs." These include:

- Agastache rugosa

Alangium chinense
Anemone or Pulsatilla chinensis
Anisodus tanguticus
Ardisia japonica
Aster tataricus
Astragalus membranaceus
Camellia sinensis
Cannabis sativa
Carthamus tinctorius
Cinnamomum cassia
Cissampelos pareira
Coptis chinensis
Corydalis ambigua
Croton tiglium
Daphne genkwa
Datura metel
Datura tatula
Dendrobium nobile
Dichroa febrifuga
Ephedra sinica
Eucommia ulmoides
Euphorbia pekinensis
Flueggea suffruticosa (formerly Securinega suffruticosa)
Forsythia suspensa
Gentiana loureiroi
Gleditsia sinensis
Glycyrrhiza uralensis

Hydnocarpus anthelmintica (syn. H. anthelminthicus)
Ilex purpurea
Leonurus japonicus
Ligusticum wallichii
Lobelia chinensis
Phellodendron amurense
Platycladus orientalis (formerly Thuja orientalis)
Pseudolarix amabilis
Psilopeganum sinense
Pueraria lobata
Rauwolfia serpentina
Rehmannia glutinosa
Rheum officinale
Rhododendron tsinghaiense
Saussurea costus
Schisandra chinensis
Scutellaria baicalensis
Stemona tuberosa
Stephania tetrandra
Styphnolobium japonicum (formerly Sophora japonica)
Trichosanthes kirilowii
Wikstroemia indica

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See also

- Herbalism, for the use of medicinal herbs in other traditions.

Drug reaction testing

Drug reaction testing uses a genetic test to predict how a particular person will respond to various prescription and non-prescription medications. It checks for genes that code for specific liver enzymes which activate, deactivate, or are influenced by various drugs.

There are currently four genetic markers commonly tested for: 2D6, 2C9, 2C19, and 1A2.

This testing has been done for some time by drug companies working on new drugs, but is relatively newly available to the general public. Strattera is the first drug to mention the test in the official documentation, although it doesn't specifically recommend that patients get the test before taking the medication.

There are four possible categories for each marker: poor metabolizer, intermediate metabolizer, extensive metabolizer, or ultra-extensive metabolizer. Different testing companies may call these by different names. Extensive metabolizers (that is, people who are extensive metabolizers of a given type) are the most common, and are the type of people for which drugs are designed. Up to 7% of Caucasians are poor metabolizers of drugs metabolized by the CYP2D6 enzyme.[1]

People who can't metabolize a drug will require a much lower dose than is recommended by the manufacturer, and those who metabolize it quickly may require a higher dose. Some drugs, such as codeine, will not be effective in people without the requisite enzymes to activate them.

People who are poor metabolizers of a drug may overdose while taking less than the recommended dose.

See also

- Medical prescription

References and End Notes

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Essential medicines

Essential medicines, as defined by the World Health Organization are "those drugs that satisfy the health care needs of the majority of the population; they should therefore be available at all times in adequate amounts and in appropriate dosage forms, at a price the community can afford."

The WHO has published a model list of essential medicines. Each country is encouraged to prepare their own lists taking into consideration local priorities. At present over 150 countries have published an official essential medicines list.The WHO List contains a core list and a complementary list.

The core list presents a list of minimum medicine needs for a basic health care system, listing the most efficacious, safe and cost-effective medicines for priority conditions. Priority conditions are selected on the basis of current and estimated future public health relevance, and potential for safe and cost-effective treatment.

The complementary list presents essential medicines for priority diseases, for which specialized diagnostic or monitoring facilities are needed. In case of doubt medicines may also be listed as complementary on the basis of consistent higher costs or less attractive cost-effectiveness in a variety of settings.

The compilation of an essential medicines list enables health authorities, especially in developing countries, to optimize pharmaceutical resources.

Pharmacist

Pharmacists are health professionals who practice the art and science of pharmacy. In their traditional role, pharmacists typically take a request for medicines from a prescribing health care provider in the form of a medical prescription and dispense the medication to the patient and counsel them on the proper use and adverse effects of that medication. In this role, pharmacists ensure the safe and effective use of medications. Pharmacists also participate in disease state management, where they optimise and monitor drug therapy – often in collaboration with physicians and/or other health professionals. Pharmacists have many areas of expertise and are a critical source of medical knowledge in clinics, hospitals, and community pharmacies throughout the world.

Pharmacists are sometimes small-business owners, owning the pharmacy in which they practice. They are also very skilled and specialized individuals with specific knowledge that makes them a vital part of any healthcare team. They act as a learned intermediary between patients and physicians to ensure that proper medical therapy is chosen and implemented in the best way possible.

Pharmacists are sometimes referred to as *chemists* (or *dispensing chemists*), which sometimes causes confusion with scientists in the field of chemistry. This term is a historical one, since pharmacists originally were required to complete an undergraduate degree in Pharmaceutical Chemistry (PhC) and were known as "Pharmaceutical Chemists".

Qualifications and registration

The basic requirement for pharmacists to be considered for registration is an undergraduate or postgraduate Pharmacy degree from a recognised university. In most countries this involves a four-year course to attain a Bachelor of Pharmacy (BPharm) degree.

In order to practise as a pharmacist, the person must be registered with the relevant statutory body, which governs the registration and practice of pharmacy within the territory of its jurisdiction. There is often a requirement for the pharmacy graduate to have completed a certain number of hours of experience in a pharmacy, under the supervision of a registered pharmacist. The statutory body will usually administer a written and oral examination to the prospective pharmacist prior to registration.

Pharmacists are trained in fields including pharmacology, chemistry, pharmaceutical chemistry, pharmacy practice (including drug interactions, medicine monitoring, medication management), pharmaceutics, pharmacy law, physiology, anatomy, biochemistry, kinetics, nephrology, hepatology, and compounding medications. Additional curriculum covers basic diagnosis with emphasis on disease state management, therapeutics and prescribing (selecting the most appropriate medication for a given patient).

Australia

In Australia, apart from the four-year BPharm course, there is the option of a postgraduate two-year Master of Pharmacy (MPharm) course for those with undergraduate science degree background.

Pharmacists are registered by Pharmacy Boards in individual states such as the Pharmacy Board of New South Wales. In Western Australia, pharmacists are registered by the Pharmaceutical Council of Western Australia. Individual states have differing requirements for pharmacy graduates for registration, but generally graduates are required to complete approximately one year of practice under the supervision of a registered pharmacist. In addition, graduates are required to complete an approved graduate training course for that state, for example the Pharmacist Graduate Training Course (PGTC) offered by the Pharmaceutical Society of Australia NSW Branch is required in New South Wales. On meeting these requirements, graduates are eligible to sit the registration examination which may involve both written and oral components.

Greece

In Greece, a five-year University course must be completed. This course is offered by the University of Athens, the University of Thessaloniki and the University of Patras. The course comprises 4 years of theory and laboratory practice and a 5th year of compulsory, full-time in-service training in a community pharmacy and the pharmaceutical department of a hospital. An additional trimester placement in a pharmaceutical industry is also an option, however it does not count towards the acquisition of the licence to practice. Upon successful completion of the course, a Degree in Pharmacy is awarded.

The pharmacy graduate may pursue a career in the industry after graduation. A career in this field does not require a licence to practise pharmacy. However, pharmacists wishing to open a pharmacy, work in hospitals or in the National Organization of Medicines must first successfully participate in board examinations organized by the Greek Ministry of Health, in order to obtain a License to Practice Pharmacy.

New Zealand

In New Zealand, as with other western nations, a four year BPharm must be completed, followed by an internship at a pharmacy. Pharmacists are registered at the Pharmaceutical Society Of New Zealand. The degree can be taken at University Of Otago in Dunedin and University Of Auckland in Auckland.

Republic of Ireland

In the Republic of Ireland, a 4-year BPharm degree must be completed followed by one year of post-registration training. Trinity College, Dublin was the only university offering the BPharm course in the Irish Republic until recently. In 2003 two new Schools of Pharmacy were opened. A Pharmacy department was created at University College, Cork on the southern coast of Ireland as well as another Pharmacy school in the Irish capital, Dublin. (Royal College of Surgeons in Ireland)

Spain

In Spain, the Degree in Pharmacy (called licenciatura en farmacia) is consisting of 5 years. Last one is divided into two semesters, first one is similar as previous years (theory and laboratory practice) but second one is a full-time in-service training in a community pharmacy or at the pharmaceutical department of a hospital. This estructure is changing by another according to European Higher Education Area's System.

After obtaining degree certificate, there is the chance of opening a pharmacy sitting an examination in order to achieve a licence. There is also the chance of postgraduate programs as Masters and Doctorates and of carrying hospital/industry speciality programs out (FIR or farmacéutico interno-residente, pharmacist intern-resident) by means of an examination like medical specialities (MIR). These specialities are: "Hospital pharmacist", "Clinical microbiology and parasitology", "Clinical biochemistry", "Clinical immunology", "Clinical analysis", "Radiopharmacy", "Galenical and industrial pharmacy" and "Drug and medicines' control and analysis".

There are 15 universities with licenciatura in Pharmacy in Spain, three of them are private universities.

United Kingdom

In the United Kingdom, integration with the European Union has resulted in the BPharm course being superseded by a four-year course for the qualification Master of Pharmacy (MPharm). In Great Britain the Royal Pharmaceutical Society of Great Britain is responsible for regulation of pharmacy affairs and in Northern Ireland it is the Pharmaceutical Society of Northern Ireland. Graduates must complete one year of practical training and pass a registration examination before they can be entered on the register of pharmacists, known as the register of pharmaceutical chemists.

Pharmacists registered in other countries can also register in the UK. Overseas pharmacists are required to undertake the Overseas Pharmacists Assessment Programme (OSPAP), a one year intensive course focused on pharmacy practice in Great Britain. OSPAP authorisation can be given by Royal Pharmaceutical Society of Great Britain and the course is undertaken either the University of Sunderland, Aston University or the University of Brighton. However, pharmacists that have obtained their qualifications and are registered in other countries of the European Economic Area can register with the Royal Pharmaceutical Society of Great Britain without undergoing additional or pre-registration training.

The term pharmacist is protected in the United Kingdom. It can only be used by individuals that are registered with the Royal Pharmaceutical Society of Great Britain.

United States

Traditionally in the United States, the bachelor's degree in pharmacy was the first-professional degree for pharmacy practice. However, in 1990, the American Association of Colleges of Pharmacy (AACP) mandated that a doctor of pharmacy would be the new first-

professional degree. As of the year 2000, all pharmacy schools in the U.S. have discontinued the B.S. Pharm. (Bachelor of Science in Pharmacy) degree program.

Today, individuals seeking to become pharmacists must first complete a pre-pharmacy undergraduate program. This program consists of a minimum of 60-70 semester credit hours (90-100 quarter credit hours) of undergraduate coursework in basic and advanced sciences; however many students go on to complete a four year program (between 120-130 semester credit hours) leading to a Bachelor of Science degree in biology, chemistry, or a similar field. In addition, a high PCAT (Pharmacy College Admission Test) score is required at most colleges and schools of pharmacy.

After admission, a student will complete a four year pharmacy program and will be awarded the Doctor of Pharmacy (PharmD) degree upon graduation. A pharmacy graduate may choose to complete an optional post-graduate residency (one to three years) or enter directly into pharmacy practice, e.g., community (retail), compounding, consultant (nursing home), hospital, nuclear, etc.

Pharmacy school graduates must complete internship requirements and pass the North American Pharmacist Licensure Examination, or NAPLEX, and an additional state exam before they can acquire a license to practice pharmacy in that state. The NAPLEX was created by the National Association of Boards of Pharmacy (NABP).

Roles

Pharmacists are often the first point-of-contact for patients with health inquiries. This means that pharmacists have large roles in the primary healthcare of patients.

These roles include, but are not limited to :

- clinical medication management
- specialized monitoring of simple and complex disease states
- reviewing medication regimens
- monitoring of treatment regimens
- general health monitoring
- compounding medicines
- general health advice
- providing specific education to patients about disease states and medications
- oversight of dispensing medicines on prescription
- provision of non-prescription medicines
- counseling and advice on optimal use of medicines
- advice and treatment of common ailments
- referral to other health professionals if necessary
- dosing drugs in renal and hepatic failure
- pharmacokinetic evaluation
- education of physicians on medications and their proper use
- prescribing medications in collaboration with other healthcare professionals
- providing pharmaceutical information

Specialities

Practice specialisation

Specialties exist within the pharmacy profession, with the place of occupation being the major differentiator. Specialities include:

- Academic pharmacist
- Clinical pharmacist
- Community pharmacist
- Compounding pharmacist
- Consultant pharmacist
- Drug information pharmacist
- Home Health pharmacist
- Hospital pharmacist
- Industrial pharmacist
- Locum pharmacist
- Regulatory-affairs pharmacist
- Veterinary pharmacist

Specialty Practice accreditation

In the United States, a pharmacist can become certified in recognized specialty practice areas by passing an examination administered by the Board of Pharmaceutical Specialties. There are five specialties in which a pharmacist can become Board-certified. The Pharmacotherapy specialty also has two subspecialties, as follows:

- Nuclear Pharmacy
- Nutrition Support Pharmacy
- Oncology Pharmacy
- Pharmacotherapy
  - Cardiology
  - Infectious disease
- Psychiatric Pharmacy

Additionally, other certifications are available from smaller credentialing boards, such as the Certified Geriatric Pharmacist (CGP) designation, administered by the Commission for Certification in Geriatric Pharmacy (CCGP).

In Australia, accreditation exists only for certain specialties and is provided by professional bodies for the following:

- Consultant Pharmacist (AACPA), by the Australian Association of Consultant Pharmacy (AACP)
- Certified Geriatric Pharmacist (CGP), by the Society of Hospital Pharmacists of Australia (SHPA)

See also

- Pharmacy

Self-medication

Self-medication is the use of drugs, sometimes illicit, to treat a perceived or real malady, often of a psychological nature.

Over-the-counter drugs are a form of self medication. The buyer diagnoses their own illness and buys a specific drug to treat it. The World Self-Medication Industry (WSMI) define self-medication as the treatment of common health problems with medicines especially designed and labeled for use without medical supervision and approved as safe and effective for such use.

A person may also self-medicate by taking more or less than the recommended dose of a drug.

Some mental illness sufferers attempt to correct their illnesses by use of tobacco, cannabis, or other mind-altering drugs. While this may provide immediate relief of some symptoms such as anxiety, it may evoke and/or exacerbate some symptoms of several kinds of mental illnesses that are already latently present, and may lead to addiction/dependence, among other side effects of long-term use of the drug. The theory that drug dependence or addiction results from self-medication for the distress caused by a pre-existing condition was introduced in 1974 by David F. Duncan and Edward J. Khantzian in independent publications. This theory has come to be known as the self-medication hypothesis. For example, sufferers of post-traumatic stress disorder are prone to self-medication, as well as many individual without this diagnosis which have suffered from (mental) trauma.

Occasionally an individual will attempt self-medication for physical illnesses. For example, it is believed that Kurt Cobain's use of heroin partially stemmed from a painful stomach condition.

The current phenomenon in many Western societies of the widespread usage of vitamins, herbs, and other over-the-counter "supplements"--usually without the advice, supervision, or even knowledge of any licensed health professional--is another possible example of self-medication. Some observers of health behavior and medical affairs have speculated that this trend may arise from the desire of laymen to feel more in control of their own health--rather than relying on the traditional medical establishment, whose motives are sometimes seen as suspect. The extraordinary increases in the cost of traditional health care in recent decades--doctors, hospitals, prescriptions, etc.-- causes some individuals to desperately try to find more affordable alternatives to treat or prevent their own afflictions, though this pursuit sometimes proves to be ineffective and expensive.

Adverse effect

In medicine, an *adverse effect* is an abnormal, harmful, undesired and/or unintended side-effect, although not necessarily unexpected, which is obtained as a result of a therapy or other medical intervention, such as drug/chemotherapy, physical therapy, surgery, medical procedure, use of a medical device, etc. Iatrogenesis (literally, generated by a physician) is a common cause of adverse effects, as well as medical error. Using a drug or other medical intervention which is contraindicated may increase the risk of adverse effects. Adverse effects may cause medical complications of a disease or procedure and negatively affect its prognosis.

The harmful outcome is usually indicated by some result such as morbidity, mortality, alteration in body weight, levels of enzymes, loss of function or as a pathological change detected at the microscopic, macroscopic or physiological level. They may cause a reversible or irreversible change, including an increase or decrease in the susceptibility of the individual to other chemicals, foods, or procedures (e.g. drug interaction).

Reporting systems

In many countries, adverse effects are required by law to be reported, researched in clinical trials and included into the patient information accompanying medical devices and drugs for sale to the public.

UK

The Yellow Card Scheme is a UK initiative run by the Medicines and Healthcare products Regulatory Agency (MHRA) and the Commission on Human Medicines (CHM) to gather information on adverse effects to medicines. This includes all licensed medicines from medicines issued on prescription to medicines bought over the counter from a supermarket. The Scheme also includes all herbal preparations and unlicensed medicines found in cosmetic treatments. ADRs can be reported by a number of healthcare professionals including doctors, pharmacists and nurses, as well as patients.

For further information see the Yellow Card Scheme website, or find copies of the Yellow Card in the appedices of a BNF.

To read reports from the UK Yellow Card Scheme you can download here.

USA

In the USA several reporting systems have been built, such as the Vaccine Adverse Event Reporting System (VAERS), the Manufacturer and User Facility Device Experience Database (MAUDE) and the Special Nutritionals Adverse Event Monitoring System. MedWatch is the main reporting center, operated by the Food and Drug Administration.

Australia

In Australia, adverse effect reporting is administered by the Adverse Drug Reactions Advisory Committee (ADRAC), a subcommittee of the Australian Drug Evaluation Committee (ADEC). Reporting is voluntary, and ADRAC requests health professionals to report all adverse reactions to its current drugs of interest, and serious adverse reactions to any drug. ADRAC publishes the Australian Adverse Drug Reactions Bulletin every 2 months.

Adverse effects of medical procedures

Surgery, of course, may have a number of undesirable or harmful after effects, such as infection, hemorrhage, inflammation, scarring, loss of function, changes in local blood flow, and so on. They can be reversible or irreversible, and a compromise must be found by the physician and the patient between the beneficial or life-saving consequences of surgery versus its adverse effects. For example, a limb may be lost to amputation in case of untreatable gangrene, but life is saved. Presently, one of the greatest advantages of minimally invasive surgery, such as laparoscopic surgery is the reduction of adverse effects.

Other non-surgical physical procedures such as high intensity radiotherapy may cause burns and alterations in the skin. In general, these therapies try to avoid damage to healthy tissues while maximizing the therapeutic effect.

Vaccination is a medical procedure which is particularly prone to adverse effects, due to the nature of its biological preparation (sometimes using attenuated pathogens and toxins). Common adverse effects may be fever, malaise and local reactions in the vaccination site, such as eczema vaccinatum, a severe, sometimes fatal complication which may result in persons who have eczema or atopic dermatitis, and, as such, those persons should not be vaccinated, even if the condition is currently not active.

Diagnostic procedures may also have adverse effects, depending much on whether they are invasive, non-invasive or minimally invasive. For example, allergic reactions to x-ray contrasting material often occur, a colonoscopy may cause the perforation of the intestine wall, etc.

Adverse effects of drugs

Main article: adverse drug reaction

Adverse effects can occur as a collateral or side effect of many interventions, but they are particularly important in pharmacology, due to its wider, and sometimes uncontrollable, use by way of self-medication. Thus, responsible drug use becomes an important issue here.

Adverse effects, like intended effects of drugs, are a function of dosage or drug levels at the target organs, so they may be avoided or decreased by means of careful and precise pharmacodynamics (the change of drug levels in the organism in function of time after administration).

Adverse effects may also be caused by drug interaction, i.e., when physicians fail to check for all medicaments a patient is taking and prescribe new ones which interact agonistically or antagonistically (potentiate or decrease the intended therapeutic effect). Significant morbidity and mortality is caused around the world because of this. Drug-drug and food-drug interactions may occur, and even so-called "natural drugs" used in alternative medicine may have dangerous adverse effects. For example, extracts of St. John's wort (Hypericum perforatum), a phytotherapic used for treating mild depression are known to cause an increase in the cytochrome P450 enzymes responsible for the metabolism and elimination of many drugs, so that patients taking it are likely to experience a reduction in blood levels of drugs that they are taking for other purposes, such as cancer chemotherapeutic drugs, protease inhibitors for HIV and oral contraceptives.

The scientific field of activity associated with drug safety is increasingly government-regulated and is of major concern for the public as well as to drug manufacturers. The distinction between adverse and non-adverse effects is a major undertaking when a new drug is developed and tested before marketing it. This is done in toxicity studies to determine the non-adverse effect level (NOAEL). These studies are used to define the dosage to be used in human testing (phase I) as well as to calculate the maximum admissible daily intake. Imperfections in clinical trials, such as insufficient number of patients or short duration, sometimes lead to public health disasters such as those of fenfluramine (the so-called fen-phen episode), thalidomide and, more recently, of cerivastatin (Baycol®, Lipobay®) and

rofecoxib (Vioxx®), where drastic adverse effects were observed, like teratogenesis, pulmonary hypertension, stroke, heart disease, neuropathy, etc., and a significant number of deaths, causing the forced or voluntary withdrawal of the drug from the market.

Most drugs have a large list of non-severe or mild adverse effects which do not rule out the interruption of usage. These effects have widely variable incidence, according to individual sensitivity. They comprise nausea, dizziness, diarrhea, malaise, vomit, headache, dermatitis, dry mouth, etc.

Controversies

Sometimes, putative medical adverse effects are regarded as controversial and generate heated discussions in society and lawsuits against drug manufacturers. One example is the current controversy whether autism may be caused by the MMR vaccine (or by thimerosal, a mercury-based preservative used in some vaccines). No significant link has been decisively found so far; nevertheless lawsuits have been brought. Another instance is the potential adverse effects of silicone breast implants, which lead to hundreds of thousands of litigations against manufacturers of gel-based implants, due to allegations of damage to the immune system which have not yet been conclusively proven.

Due to the exceedingly high impact on public health of widely used medications, such as oral contraceptives and hormone replacement therapy, which may affect millions of users, even marginal probabilities of adverse effects of a severe nature, such as breast cancer, have led to public outcry and changes in medical therapy, although its benefits largely surpassed the statistical risks.

Limitations of adverse effects reporting

In principle, medical professionals are required to report all adverse effects related to a specific form of therapy. In practice, it is at the discretion of the professional to determine whether a medical event is at all related to the therapy. For example, a leg fracture in a skiing accident in a patient who years before took antibiotics for pneumonia is not likely to get reported.

As a result, routine adverse effects reporting may often not include long-term and subtle effects that may ultimately be attributed to a therapy.

Examples of adverse effects

- Abortion, miscarriage or uterine hemorrhage associated with misoprostol (Cytotec®), a labor-inducing drug (this is a case where the adverse effect has been used legally and illegally for performing abortions)

Addiction to many sedatives and analgesics such as diazepam, morphine, etc.
Bleeding of the intestine associated with aspirin therapy
Deafness and kidney failure associated with gentamicin (an antibiotic)
Death, following sedation in children using propofol (Diprivan®)
Dementia associated with heart bypass surgery
Depression or hepatic injury caused by interferon

Diabetes caused by atypical antipsychotic medications (neuroleptic psychiatric drugs)
Diarrhea caused by the use of orlistat (Xenical®)
Erectile dysfunction associated with many drugs, such as antidepressants
Fever associated with vaccination (in the past, imperfectly manufactured vaccines, such as BCG and poliomyelitis, have caused the very disease they intended to fight).
Glaucoma associated with corticosteroid-based eye drops
Hair loss and anemia may be caused by chemotherapy against cancer, leukemia, etc.
Headache following spinal anesthesia
Hypertension in ephedrine users, which prompted FDA to remove the status of dietary supplement of ephedra extracts
Insomnia caused by stimulants, Ritalin®, Adderall®, etc.
Lactic acidosis associated with the use of stavudine (Zerit®, for anti-HIV therapy) or metformin (for diabetes)
Melasma and thrombosis associated with oral contraceptive use
Rhabdomyolysis associated with statins (anti-cholesterol drugs)
Seizures caused by withdrawal from benzodiazepine
Sleepiness or increase in appetite due to antihistamine use
Stroke or heart attack associated with sildenafil (Viagra®) when used with nitroglycerine
Suicide, increased tendency associated to the use of fluoxetine and other SSRI antidepressants
Tardive dyskinesia associated with long-term use of metoclopramide and many antipsychotic medications

See also

- Medical prescription

Agonist

An *agonist* is a molecule that selectively binds to a specific receptor and triggers a response in the cell. It mimicks the action of an endogenous biochemical molecule (such as hormone or neurotransmitter) that binds to the same receptor. It is a drug molecule (synthesized outside an organism) that reproduces the action of an endogenous natural biochemical (synthesized inside an organism). An agonist is the opposite of an antagonist in the sense that while an antagonist also binds to the receptor, the antagonist does not activate the receptor and actually blocks it from activation by agonists. A *partial agonist* (such as buspirone, aripiprazole, bifeprunox or norclozapine) activates a receptor, but only produces a partial physiological response compared to a *full agonist*. A *co-agonist* works with other co-agonists to produce the desired effect together. Receptors can be activated or inactivated by

endogenous (such as hormones and neurotransmitters) or exogenous (such as drugs) agonists and antagonists, resulting in stimulating or inhibiting the cell. To see how an agonist may activate a receptor see this link. Recently a novel theory called Functional Selectivity has been proposed that broadens the conventional definition of pharmacology.

Etymology

Stems from the Greek agonistes, 'contestant', from agon, 'contest'. An agonist is a chemical contestant or contender.

See also

- Receptor antagonist

Placebo

A *placebo*, from the Latin for "I shall please", is an inactive substance (pill, liquid, etc.), which is administered as if it were a therapy, but which has no therapeutic value other than the placebo effect.

Early use of placebos

Originally, a placebo was a substance that a well-meaning doctor would give to a patient, telling him that it was a powerful drug (e.g., a painkiller), when in fact it was nothing more than a sugar pill. Thus, Hooper's medical dictionary of 1811 says placebo is "an epithet given to any medicine adapted more to please than benefit the patient." The subsequent reduction of the patient's symptoms was attributed to the patient's belief in the drug.

Placebos are themselves inactive, however a patient may experience either a positive or negative clinical effect while taking one. When a placebo is administered to mimic a previously administered drug, it may also incur the same side effects as the prior authentic drug. Most of these effects are thought to be psychological in nature or due to other unrelated factors. Not all placebos are "created equal." A placebo that involves ingestion, injection, or incision is often more powerful than a non-invasive technique. Placebos administered by authority figures such as general practitioners and other experts may also be more powerful than when the psychological authority effect is absent.

A placebo which results in a worsening of symptoms is called a nocebo (Latin for "I will harm").

Modern clinical application

Experimenters typically use placebos in the context of a clinical trial, in which a "test group" of patients receives the therapy being tested, and a "control group" receives the placebo. It can then be determined if results from the "test" group exceed those due to the

placebo effect. If they do, the therapy or pill given to the "test group" is assumed to have had an effect. The first well documented use of a placebo in a clinical trial was reported in "Streptomycin treatment of pulmonary tuberculosis". BMJ 1948;2:769--782, a research paper by the Medical Research Council. Thus, if a therapy or medicine has no effect beyond placebo, then it is said to have no effect or efficacy beyond non-specific effects.

Technical challenges and pitfalls

Double-Blinding

Appropriate use of a placebo in a clinical trial often requires or at least benefits from a double-blind study design, which means that neither the experimenters nor the subjects know which subjects are in the "test group" and which are in the "control group". This sometimes causes difficulties as a double-blind design cannot be easily applied to many treatments. For example, because some drugs have clear physiological impact, an inert pill (e.g., a sugar pill) would not be an effective placebo to test against any such drug. That is, an inert pill could not be used to demonstrate whether an active drug with noticeable physical side effects has more than a strong placebo effect. For example, long before any psychoactive response most people can tell if they have ingested an active antidepressant or anti-anxiety agent because of their physiological effects. The same is true of strong pain relievers. Believing you have received the active drug can produce a markedly heightened placebo effect. To offset this heightened effect, it is necessary to use a *psychoactive placebo,* i.e., a drug that produces enough physical effects to balance the belief in the control and experimental groups that they have received the active drug. An example of the use of a psychoactive placebo can be found in the Marsh Chapel Experiment. In that double-blind study, the experimental group received psilocybin while the control group received a large dose of niacin that produces noticeable physical effects.

Measuring the Placebo Effect

Ethical challenges and concerns

Bioethicists have raised diverse concerns on the use of placebos in modern medicine and research. These have been largely incorporated into modern rules for the use of placebos in research but some issues remain subject to debate.

- Disclosure. Rules that govern modern clinical trials insist on full disclosure to subjects who take part. Today, subjects are told that they may receive the drug being tested or they may receive the placebo.
- Balancing Treatment vs. Research Objectives. Ethicists have also raised concerns on the use of placebos in those circumstances in which a standard treatment exists unless there are genuine doubts of the effectivity of such standard treatment. If standard treatments exist for the disease being studied in clinical trials, a standard treatment is always used in place of a placebo for serious diseases.

See also

- Placebo effect

Placebo effect

The *placebo effect* (Latin placebo, "I shall please"), first mentioned in 1955 by Henry K. Beecher, M.D. (Beecher 1955) and also known as non-specific effects and the subject-expectancy effect, is the phenomenon that a patient's symptoms can be alleviated by an otherwise ineffective treatment, since the individual expects or believes that it will work. Some people consider this to be a remarkable aspect of human physiology; others consider it to be an illusion arising from the way medical experiments were conducted. The phenomenon, if it exists at all, is not fully understood by science.(New Scientist Space 19 March 2005)

In the opposite effect, a patient who disbelieves in a treatment may experience a worsening of symptoms. This nocebo effect (Latin nocebo, "I shall harm") can be measured in the same way as the placebo effect, e.g., when members of a control group receiving an inert substance report a worsening of symptoms. The recipients of the inert substance may nullify the placebo effect intended by simply having a negative attitude towards the effectiveness of the substance prescribed, which often leads to a nocebo effect, which is not caused by the substance itself, but more the patient's mentality towards her or his ability to get well.

Placebo-controlled studies

Beecher (1955) reported that about a quarter of patients who were administered a placebo, for example against back pain, reported a relief or diminution of pain. Remarkably, not only did the patients report improvement, but the improvements themselves were often objectively measurable, and the same improvements were typically not observed in patients who did not receive the placebo.

Because of this effect, government regulatory agencies approve new drugs only after tests establish not only that patients respond to them, but also that their effect is greater than that of a placebo (by way of affecting more patients, by affecting responders more strongly or both). Such a test or clinical trial is called a placebo-controlled study. Because a doctor's belief in the value of a treatment can affect his or her behaviour, and thus what his or her patient believes, such trials are usually conducted in "double-blind" fashion: that is, not only are the patients made unaware when they are receiving a placebo, the doctors are made unaware too. Recently, it has even been shown that "mock" surgery can have similar effects, and so some surgical techniques must be studied with placebo controls (rarely double blind, due to the difficulty involved). To merit approval, the group receiving the experimental treatment must experience a greater benefit than the placebo group.

Nearly all studies conducted this way show some benefit in the placebo group. For example, Khan published a meta-analysis of studies of investigational antidepressants and found a 30% reduction in suicide and attempted suicide in the placebo groups and a 40% reduction in the treated groups. (Khan 2000) However, studies generally do not include an *untreated* group, so determining the actual size of the placebo effect, compared to totally untreated patients, is difficult.

Notable placebo effect absences

In psychological treatment, two disorders are known to have very low placebo effects: schizophrenia, and obsessive compulsive disorder.

Placebo and pain

Careful studies have shown that the placebo effect can alleviate pain, although the effect is more pronounced with pre-existing pain than with experimentally induced pain. People can be conditioned to expect analgesia in certain situations. When those conditions are provided to the patient, the brain responds by generating a pattern of neural activity that produces objectively quantifiable analgesia. (Benedetti 2003, Wager 2004)

Evans argued that the placebo effect works through a suppression of the acute phase response, and as a result does not work in medical conditions that do not feature this. (Evans 2005) The acute phase response consists of inflammation and sickness behaviour:

- Four classic signs of ‘inflammation’: tumor, rubor, calor and dolor – swelling, redness, heat and pain.
- Sickness behaviour: lethargy, apathy, loss of appetite and increased sensitivity to pain.

Placebo and depression

A brain-imaging study found that depressed patients who responded to the placebo effect showed changes in cerebral blood flow, which were similar to the changes in brain function seen in patients who responded to anti-depressant medication. (Leuchter 2002) Other studies argue that up to 75% of the effectiveness of anti-depressant medication is due to the placebo-effect rather than the treatment itself. (Khan 2000)

Endogenous Opiates

Endogenous opiates are chemicals produced by the brain that suppress pain and produce analgesia and a sense of well-being. Opium and drugs derived from it (opiates) produce their "highs" by triggering the same brain receptors used by natural opiates. Increased release of endogenous opiates like endorphin is associated with pleasant experiences like exercise (the runner's high) and sex. When patients who claimed to experience pain relief after receiving a placebo were injected with naloxone (a drug that blocks the effects of opiates), their pain

returned, suggesting that the placebo effect may be partly due to the release of natural opiates. (Sauro 2005)

Objective or subjective effects?

Hrobjartsson and Götzsche published a study in 2001 and a follow-up study in 2004 questioning the nature of the placebo effect. (Hrobjartsson 2001, Hrobjartsson 2004) They performed two meta-analyses involving 156 clinical trials in which an experimental drug or treatment protocol was compared to a placebo group and an untreated group, and specifically asked whether the placebo group improved compared to the untreated group. Hrobjartsson and Götzsche found that in studies with a binary outcome, meaning patients were classified as improved or not improved, the placebo group had no statistically significant improvement over the no-treatment group. Similarly, there was no significant placebo effect in studies in which objective outcomes (such as blood pressure) were measured by an independent observer. The placebo effect could only be documented in studies in which the outcomes (improvement or failure to improve) were reported by the subjects themselves. The authors concluded that the placebo effect does not have "powerful clinical effects," (objective effects) and that patient-reported improvements (subjective effects) in pain were small and could not be clearly distinguished from bias.

These results suggest that the placebo effect is largely subjective. This would help explain why the placebo effect is easiest to demonstrate in conditions where subjective factors are very prominent or significant parts of the problem. Some of these conditions are headache, stomachache, asthma, allergy, tension, and the experience of pain, which is often a significant part of many mild and serious illnesses.

How the placebo effect works

There are three main hypotheses for how the placebo effect works, the subject-expectancy effect, conditioning and motivation.

Expectancy Effect

The subject-expectancy effect attributes the placebo effect to conscious or unconscious manipulation by patients in reporting improvement. Hrobjartsson and Götzsche argued in their article, "Most patients are polite and prone to please the investigators by reporting improvement, even when no improvement was felt." Subjective bias can also be unconscious, where the patient believes he is improving as a result of the attention and care he has received.

Conditioning

Classical conditioning is a type of associative learning where the subject learns to associate a particular stimulus with a particular response. In this case the stimulant is the substance perceived as medicine but is the placebo, and the response is the relief of

symptoms. It is difficult to tell the difference between conditioning and the expectancy effect when the outcome is subjective and reported by the patient. However, conditioning can result in measurable biological changes similar to the changes seen with the real treatment or drug. For example, studies showing that placebo treatments result in changes in brain function similar to the real drug are probably examples of conditioning resulting in objectively measurable results. (Sauro 2005, Wager 2004, Leuchter 2002)

Motivation

Motivational explanations of the placebo effect have typically considered the placebo effect to be an outcome of one's desire to feel better, reduce anxiety, or cooperate with an experimenter or health care professional (Price et al. 1999, Margo 1999). The motivational perspective is supported by recent research showing that nonconscious goals for cooperation can be satisfied by confirming expectations about a treatment (Geers et al. 2005).

The use of placebos in medical practice

The ethics of prescribing placebos in medical practice is highly debated. Some practitioners argue that the use of placebos is sometimes justified because it will do no harm and may do some good. With the publication of studies by Hróbjartsson and Götzsche and others, the proposition that placebos may do some good is under fire.

In research experimental studies, the method of establishing a proper control group to eliminate the placebo effect has also been difficult, particularly for surgical and therapy interventions that are not pharmaceutical in nature. Notably, there has been much debate of whether to use a placebo pill or conduct a sham procedure as a control.

A study of Danish general practitioners found that 48% had prescribed a placebo at least 10 times in the past year. The most frequently prescribed placebos were antibiotics for viral infections, and vitamins for fatigue. Specialists and hospital-based physicians reported much lower rates of placebo use. (Hrobjartsson 2003) A 2004 study in the British Medical Journal of physicians in Israel found that 60% used placebos in their medical practice, most commonly to "fend off" requests for unjustified medications or to calm a patient. Of the physicians who reported using placebos, only 15% told their patients they were receiving placebos or non-specific medications. (Nitzan 2004) An accompanying editorial stated,

"The placebo effect, thought of as the result of the inert pill, can be better understood as an effect of the relationship between doctor and patient. Adding the doctor's caring to medical care affects the patient's experience of treatment, reduces pain, and may affect outcome. This survey makes it clear that doctors continue to use placebos, and most think they help."

The editorial suggested there were problems with Hróbjartsson and Götzsche's methods and argued that their results show that placebos can't cure everything, but don't prove that the placebo effect cures nothing. The editorial concluded, "We cannot afford to dispense with any treatment that works, even if we are not certain how it does." (Spiegel 2004)

The editorial prompted responses on both sides of the issue.[1]

- Critics of the practice responded that it is unethical to prescribe treatments that don't work, and that telling a patient that a placebo is a real medication is deceptive and harms the doctor-patient relationship in the long run. Critics also argued that using placebos can delay the proper diagnosis and treatment of serious medical conditions.
- Defenders of the use of placebos suggested that placebos do not work in clinical trials because the subjects know they might be getting a placebo, but do work in medical practice where the patient believes he or she is getting an active drug. Other writers pointed to the empirical data showing that placebos can have measurable biological effects, especially in pain relief (see above), or argued that the use of a placebo to "please the patient" fosters real healing as part of a caring doctor-patient relationship. (Barfod 2005, Di Blasi 2005)

About 25% of physicians in both the Danish and Israeli studies used placebos as a diagnostic tool to determine if a patient's symptoms were real, or if the patient was malingering. Both the critics and defenders of the medical use of placebos agreed that this was unethical. The BMJ editorial said, "That a patient gets pain relief from a placebo does not imply that the pain is not real or organic in origin...the use of the placebo for 'diagnosis' of whether or not pain is real is misguided."

The placebo administration may prove to be a useful treatment in some specific cases where recommended drugs can not be used. For example, burn patients who are experiencing respiratory problems cannot often be prescribed opioid (morphine) or opioid derivatives (pethidine), as these can cause further respiratory depression. In such cases placebo injections (normal saline, etc.) are of use in providing real pain relief to burn patients if they (those not in delirium) are told that are being given a powerful dose of painkiller.

There is general agreement that placebo control groups are an important tool for controlling for several types of possible bias, including the placebo effect, in double blind clinical trials.

The placebo effect is an active area of research and discussion and it is possible that a clear consensus regarding the use of placebos in medical practice will emerge in the future.

Methodology of Administration

Placebos are things like sugar pills, that look like real treatments but in fact have no physical effect. They are used to create "blind" trials in which the participants do not know whether they are getting the active treatment or not, so that physical effects can be measured independently of the participants' expectations. There are various effects of expectations, and blind trials control all of these together by making whatever expectations there are equal for all cases. Placebos aren't the only possible technique for creating blindness (unawareness of the intervention): to test the effectiveness of prayer by others, you just don't tell the participants who has and has not had prayers said for them. To test the effect of changing the frequency of fluorescent lights on headaches, you just change the light fittings at night in the absence of the office workers (this is a real case).

Related to this is the widespread opinion that placebo effects exist, where belief in the presence of a promising treatment (even though it is in fact an inert placebo) creates a real

result e.g. recovery from disease. Placebos as a technique for blinding will remain important even if there is no placebo effect, but obviously it is in itself interesting to discover whether placebo effects exist, how common they are, and how large they are. After all, if they cure people then we probably want to employ them for that.

Claims that placebo effects are large and widespread go back to at least Beecher (1955). However Kienle and Kiene (1997) did a reanalysis of his reported work, and concluded his claims had no basis in his evidence; and then Hrobjartsson & Gotzsche (2001) did a meta-analysis or review of the evidence, and concluded that most of these claims have no basis in the clinical trials published to date. The chief points of their skeptical argument are:

- Only trials that compare a group that gets no treatment with another group that gets a placebo can test the effect.
- Most claims are based on looking at the size of the improvement measured in placebo groups in trials comparing only placebo and experimental (active) treatments. This is misleading since (for instance) most diseases have a substantial clearup rate with no treatment: seeing improvements doesn't mean the placebo had an effect. (Put more technically, comparing with the baseline (pretest measure) is vulnerable to regression to the mean.)

Nevertheless, even they conclude that there is a real placebo effect for pain (not surprising since this is partly understood theoretically: Wall, 1999)); and for some other continuously-valued subjectively-assessed effects. A recent experimental demonstration was reported: Zubieta et al. (2005) "Endogenous Opiates and the Placebo Effect" The journal of neuroscience vol.25 no.34 p.7754-7762

This seems to show that the psychological cause (belief that the placebo treatment might be effective in reducing pain) causes opioid release in the brain, which then presumably operates in an analogous way to externally administered morphine.

A recent and more extensive review of the overall dispute is: M. Nimmo (2005) Placebo: Real, Imagined or Expected? A Critical Experimental Exploration Final year undergraduate Critical Review, Dept. of Psychology, University of Glasgow. PDF copy.

Summary

- Placebos are used to create blind trials. They are not the only technique for this, but are a very common and important one.
- Whether or not there is a placebo effect, placebos will remain an important technique for this.
- Recent skeptical meta-analysis of placebo effects suggest that the effect does exist, but only in very limited contexts. The widespread claims are mainly misplaced, based on faulty inferences.
- Placebos are often seen as posing ethical difficulties. Essentially the issues are of two kinds, neither about placebos alone.
    - Deceiving experimental participants, or at least withholding information. This is potentially in tension with the principle of informed consent. This is most acute for experiments that wish not just to achieve blinding, but to measure the effect of expectancies, and so wish to induce expectancies by misinforming (some) participants.

- Withholding treatment from patients (or education from students). The tension here is between the greater certainty a controlled experiment will give, versus the prior guesses of people and experts. After all, you probably wouldn't do an experiment unless you had some reason to hope a treatment worked; but if you do have such grounds, then your opinion of the best treatment should be given to all patients rather than give some a placebo.

Ways of classifying and comparing such effects Can we organize these (and other) various reported effects in some useful way? What are the effects that might be related?

Confounders mistaken for placebo effect

Due to the difficulty in ascribing causation, many phenomena overlap with — and can thus mistakenly be included in — statistics on the placebo effect.

- Natural termination of the disease process.
- Regression to the mean. Cyclical presentation of the disease.
- Errant diagnosis or prognosis.
- Temporary improvement confused with cure.

Notes

1. ^ BMJ posted a series of responses to Dr. Siegel's editorial online in their rapid response section. Selected responses were published in later issues of the Journal.

References

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Prescription drug

A *prescription drug* is a licensed medicine that is regulated by legislation to require a prescription before it can be obtained. The term is used to distinguish it from over the counter drugs which can be obtained without a prescription. Different jurisdictions have different definitions of what constitutes a prescription drug. As a general rule, over the counter drugs are used to treat conditions not necessarily requiring a doctor's care and will have been proven to meet higher safety standards for self-medication by patients. Often a lower dosage of a drug will be approved for OTC use, while higher dosages will remain the province of a doctor's prescription; a notable case is ibuprofen, which has been widely available as an OTC pain killer since the mid-1980s but is still available in doses up to four times the OTC dose for use in cases of severe orthopedic pain.

In the United States, the term "prescription drug" is most commonly used, but they are also called *legend drugs* or *Rx-only drugs*, after the requirements of Federal and state laws that all such drugs bear a "legend" prohibiting sale without a prescription; though more complex legends have been used, on most original drug packaging today the legend simply says "Rx only". In the United Kingdom, they are referred to as *Prescription Only Medicine* or *POM*.

Dispensation of prescription drugs often includes a package insert (in Europe, a Patient Information Leaflet or PIL) that gives detailed information about the drug.

Regulation in United States

In the United States, the Federal Food, Drug, and Cosmetic Act defines what requires a prescription. Prescription drugs are generally authorized by doctors, though physician assistants and nurse practitioners do an increasing amount of drug prescribing. It is generally required that an MD,DO,PA or NP write the prescription; nurses (other than nurse practitioners), emergency medical technicians, psychologists (but not psychiatrists, who are MDs), as examples, do not generally have the authority to prescribe drugs. Unlike many other countries, the United States does not have price controls for prescription drugs, and US drug prices are often perceived as inflated in comparison to other countries; therefore, most health insurance programs (generally partially or in full paid for by the patient's employer) have prescription payment plans where the patient pays only a small copayment and the pharmacy is reimbursed for the rest of the cost by the insurance company.

The safety and effectiveness of prescription drugs in the U.S. is regulated by the federal Prescription Drug Marketing Act of 1987.

Regulation in United Kingdom

In the United Kingdom, a patient visits a general practitioner who is able to prescribe medicines. If given an NHS prescription, this can be taken to a pharmacy to be dispensed. District nurses and health visitors have had limited prescribing rights since the mid-nineties where prescription for dressings and simple medicines would have had to have been signed by a doctor. Extended prescribing was introduced in late 1999, where appropriately trained nurses could prescribe from a limited list of POMs. From 2006, some nurses and pharmacists will be permitted to prescribe all medicines in the British National Formulary, except controlled drugs directly. Each item on the prescription is liable to a prescription charge of £6.65 (as of April 2006), although many patients are exempt from this charge. This includes those over 60, under 16, patients with certain medical conditions and those on certain benefits.

An HC2 ceftificate can be applied for if you are on a low income or on incapacity benefit.One bizarre element of the prescribing charges system in the UK is that if you are in reciept of "Incapacity benefit" (Due to illness)this does NOT automatically entitle you to free prescriptions.After completion of a lengthy in depth form (HC1),which means tests your ability to pay prescription charges,you may be awarded an HC2 certificate which entitles you to free prescriptons. An HC2 certificate is notoriously difficult to obtain,Why people who are on "Incapacity benefit" should pay prescription charges when they are unable to work due

to illness is a mystery.Claimants of "Jobseekers" and "Income support" automatically recieve free prescriptions and dentistry.

Those requiring regular prescriptions may make a saving by purchasing a pre-payment certificate which covers the cost of all prescriptions required for four months or a year. This charge is paid entirely to the NHS through the pharmacy, while the pharmacy claims the cost of the medicine dispensed. Each "item" can cover any prescribed item in a very large or very small quantity according to the doctor's prescription. This means that the patients perceived "value" of the charge varies enormously - the actual cost of the medicine given out will routinely vary from a few pence to hundreds of pounds.

The majority of items dispensed on NHS prescription are exempt from charges. This is because of the large number of medicines needed by, for example, the elderly or those with medical exemptions. NHS prescriptions can also be written for certain items by dentists and nurses. Some patients also receive private prescriptions, typically either from a doctor seen privately or for medicine not permitted on the NHS. For these, the patient will pay the pharmacy directly for the cost of the medicine and the pharmacy's markup.

The devolved legislature in Wales has decided to phase out prescription charges altogether; this process is expected to be completed during 2007. In January 2006, similar proposals were made by the health committee of the Scottish Parliament; however, these were rejected by Health Minister Andy Kerr on the grounds that "Executive policy remains that it is right that patients who can afford to should continue to contribute towards NHS dispensing costs".

Further reading

- Jerry Avorn, Powerful Medicines: The Benefits, Risks, and Costs of Prescription Drugs, Random House (2004), hardcover, 448 pages, ISBN 0-375-41483-5

Receptor antagonist

In medicine and biology, a *receptor antagonist* is a ligand that inhibits the function of an agonist and inverse agonist for a specific receptor.

Most drugs exert effects, both beneficial and detrimental, by interacting with specific receptors that are present on or within cells. Historically, receptors were thought to act much like light switches. Agonists were thought to turn "on" a single cellular response by binding to the receptor, thus initiating a biochemical mechanism for change within a cell. Antagonists were thought to turn "off" that response by 'blocking' the receptor from the agonist.

Recently, the discovery of inverse agonists and other concepts such as functional selectivity have blurred these definitions.

Today's current theories involving receptor antagonists center around an antagonist's ability to counteract the effects of agonists and inverse agonists (if one exists for the specific receptor). Antagonists work by binding to receptors and stopping cascades put in place by

an agonist. On their own, antagonists produce no effect by themselves to a cell, and are said to have zero intrinsic activity and zero efficacy.

There are three kinds of receptor antagonists:

- Antagonists that compete with an agonist for a binding site are competitive antagonists. They bind to the same receptor binding site as the agonist, thus competing for the same binding site. An example is the interleukin-1 receptor antagonist, IL-1Ra. High concentrations of agonist will displace the antagonist from the receptor.
- Antagonists that antagonize by other means are non-competitive antagonists. They bind to a different binding-site from the agonists, exerting their action to that receptor via the other binding site. Thus, they are called non-competitive antagonists because they do not compete for the same binding site as the agonists.
- Antagonists that bind covalently with the receptor binging site are irreversible antagonists. Unlike competitive antagonism, the covalent nature of the bond means the antagonist cannot be displaced by raising the concentration of the agonist.

Antagonists may be naturally occurring as is the case with *physiological antagonists*, or they may be synthetic and made to mimic the body's physiological antagonists. There are multiple antagonists for most receptors. A synthetic antagonist may compete with a physiological antagonist for binding sites upon receptors. Similarly, endogenous antagonists may also compete with one another. The antagonist which is bound is usually the one with the higher affinity for the receptor.

See also

- Agonist

Tablet

A *tablet* is a mixture of active substances and binders, usually in powder form, pressed into a solid.

Medicines to be taken orally are very often supplied in tablet form; indeed the word tablet without qualification would be taken to refer to a medicinal tablet. Medicinal tablets are usually called pills. Other products are manufactured in the form of tablets which dissolve; e.g., for cleaning and deodorizing.

Medicinal tablets are usually intended to be swallowed, and are of a suitable size and shape. A coating may be applied to hide the taste of the tablet's components. Tablets for other purposes, e.g., effervescent medicinal tablets and non-medicinal tablets, may be larger.

Medicinal tablets were originally made in the shape of a disk of whatever colour their components determined, but are now made in many shapes and colours to help users to distinguish between different medicines that they take. Tablets are often stamped with symbols, letters, and numbers which enable them to be identified. Sizes of tablets to be

swallowed range from a few millimeters to about a centimeter. Some tablets are in the shape of capsules, and are called "caplets".

When Tylenol (paracetamol/acetaminophen) capsules were laced with cyanide (an incident referred to as the Tylenol scare), many people stopped buying capsules because they are easy to contaminate, in favor of tablets, which are not. Some makers of OTC (over-the-counter) drugs responded by starting to make what they termed "caplets", which were actually just tablets made in the shape of a capsule.

Tablets are often scored to allow them easily to be broken into equal halves for smaller doses.

Some people have difficulty swallowing tablets, this is called dysphagia. This is often caused by a gag reflex.

Tabletting formulations

In the tablet-pressing process, it is important that all ingredients be dry, powdered, and of uniform grain size as much as possible. Mixed grain sizes tend to separate out due to operational vibrations, resulting in inconsistent tableting, while any moisture in the system will tend to clog the tableting pathways.

Some substances may be tableted as pure substances, but this is usually not the case; most formulations include excipients. Normally, an inactive ingredient termed a binder is added to help hold the tablet together and give it strength. A wide variety of binders may be used, some common ones including lactose powder, sucrose powder, tapioca starch (cassava flour) and microcrystalline cellulose.

Often, an ingredient is also needed to act as an Disintegrant. This is an ingredient that dissolves readily in water to help the tablet disperse once swallowed. Some binders, such as starch, are also excellent disintegrants.

Small amounts of lubricants are usually added, as well. The most common of these are stearic acid (stearin) and magnesium stearate. These help the tablets, once pressed, to be more easily ejected from the die.

Tablet coating

Many tablets today are coated after being pressed. Although sugar-coating was popular in the past, the process has many drawbacks. Modern tablet coatings are polymer and polysaccharide based, with plasticizers and pigments included. Tablet coatings must be stable and strong enough to survive the handling of the tablet, must not make tablets stick together during the coating process, and must follow the fine contours of embossed characters or logos on tablets. Coatings can also facilitate printing on tablets, if required. Coatings are necessary for tablets that have an unpleasant taste, and a smoother finish makes large tablets easier to swallow. Tablet coatings are also useful to extend the shelf-life of components that are sensitive to moisture or oxidation. Opaque materials like titanium dioxide can protect light-sensitive actives from photodegradation. Special coatings (for example with pearlescent effects) can enhance brand recognition.

If the active ingredient of a tablet is sensitive to acid, or is irritant to the stomach lining, an enteric coating can be used, which is resistant to stomach acid and dissolves in the high

pH of the intestines. Enteric coatings are also used for medicines that can be negatively affected by taking a long time to reach the small intestine where they are absorbed. Coatings are often chosen to control the rate of dissolution of the drug in the gastro-intestinal tract. Some drugs will be absorbed better at different points in the digestive system. If the highest percentage of absorption of a drug takes place in the stomach, a coating that dissolves quickly and easily in acid will be selected. If the rate of absoprtion is best in the large intestine or colon, then a coating that is acid resistent and dissolves slowly would be used to ensure it reached that point before dispersing. The area of the Gastro-intestinal tract with the best absorption for any particluar drug is usually determined by clinical trials.

Tablet presses

Tablet presses, the machines that make the tablets, range from small, inexpensive bench-top models that make one tablet at a time, no more than a few thousand an hour, and with only around a half-ton pressure, to large, computerized, industrial models that can make hundreds of thousands of tablets an hour with much greater pressure. Some tablet presses can make extremely large tablets, such as some of the toilet cleaning and deodorizing products or dishwasher soap. Others can make smaller tablets, from regular aspirin to some the size of a bb gun pellet. Tablet presses may also be used to form tablets out of a wide variety of materials, from powdered metals to cookie crumbs. Currently the tablet press an important piece of machinery for any manufacturer who wishes to get into pharmaceutical manufacturing.

Pill-splitters

It is sometimes necessary to split pills into halves or quarters. Tablets are easier to break accurately if scored, but there are devices called pill-splitters which cut unscored (and, obviously, also scored) pills.

Medical prescription

A *medical prescription* is an order (often in written form) by a qualified health care professional to a pharmacist or other therapist for a treatment to be provided to their patient.

Format and definition

Prescriptions are typically handwritten on preprinted prescription forms that are assembled into pads, or alternatively printed onto similar forms using a computer printer. Preprinted on the form is text that identifies the document as a prescription, the name and address of the prescribing provider and any other legal requirement such as a registration number (e.g. DEA Number in the United States). Unique for each prescription is the name of the patient. In the United Kingdom the patient's name and address must also be recorded.

Each prescription is dated and some jurisdictions may place a time limit on the prescription. There is the specific "recipe" of the medication and the directions for taking it. Finally there is the doctor's signature.

The symbol "R***x***" meaning "prescription" is a transliteration of a symbol resembling a capital R with a cross on the diagonal ***()***.

There are various theories about the origin of this symbol - some note its similarity to the Eye of Horus, others to the ancient symbol for Jupiter, both gods whose protection may have been sought in medical contexts. Alternatively, it may be intended as an abbreviation of the Latin "recipe", the imperative form of "recipere", "to take", and it is quite possible that more than one of these factors influenced its form. Literally, "Recipe" means simply "Take...." and when a doctor writes a prescription beginning with "Rx", he or she is completing the command. This was probably originally directed at the pharmacist who needed to take a certain amount of each ingredient to compound the medicine, rather than at the patient who must "take" the medicine, in the sense of consuming it.

Incidentally, in an entirely unrelated context (communications), "Rx" is an abbreviation for "receiver" or "to receive" and, in the same context, "Tx" is an abbreviation for "transmitter" or "to transmit."

The word "prescription" can be decomposed into "pre" and "script" and literally means, "to write before" a drug can be prepared. Those within the industry will often call prescriptions simply "scripts".

Contents of the prescription

Both pharmacists and physicians are regulated professions in most jurisdictions. A prescription as a communications mechanism between them is also regulated and is a legal document. Regulations may define what constitutes a prescription, the contents and format of the prescription (including the size of the piece of paper - see Exhibit C paragraph 10) and how prescriptions are handled and stored by the pharmacist. Many jurisdictions will now allow faxed or phone prescriptions containing the same information. Exhibit A below illustrates the legal definition of a prescription.

Many brand name drugs have less expensive generic drug substitutes that are chemically equivalent. Prescriptions will also contain instructions on whether the prescriber will allow the pharmacist to substitute a generic version of the drug. This instruction is communicated in a number of ways. In some jurisdictions, the preprinted prescription contains two signature lines: one line has "dispense as written" printed underneath; the other line has "substitution permitted" underneath. Some have a preprinted box "dispense as written" for the prescriber to check off (but this is easily checked off by anyone with access to the prescription). Other jurisdictions the protocol is for the prescriber to handwrite one of the following phrases: "dispense as written", "DAW", "brand necessary", "do not substitute", "no substitution", "medically necessary", "do not interchange"

As a guideline, pediatric prescriptions should include the age of the child if the patient is less than twelve and the age and months if less than five. (In general, including the age on the prescription is helpful.) In some jurisdictions, it may be a legal requirement to include the age of child on the prescription. Adding the weight of the child is also helpful.

Prescriptions often have a "label" box. When checked, pharmacist is instructed to label the medication. When not checked, the patient only receives instructions for taking the medication and no information about the prescription itself.

Some prescribers further inform the patient and pharmacist by providing the indicator for the medication; i.e. what is being treated. This assists the pharmacist in checking for errors as many common medications can be used for multiple medical conditions.

Some prescriptions will specify whether and how many "repeats" or "refills" are allowed; that is whether the patient may obtain more of the same medication without getting a new prescription from the doctor. Regulations may restrict some types of drugs from being refilled.

In group practices, the preprinted portion of the prescription may contain multiple prescribers' names. Prescribers typically circle themselves to indicate who is prescribing or there may be a checkbox next to their name.

Handling of the prescription

When filled by a pharmacist, as a matter of business practice, the pharmacist may write certain information right on the prescription. This may also be mandated by legislation (see Exhibit D). Information such as the actual manufacturer of the drug and the date the medication was dispensed may be written right onto the prescription. Legislation may require the pharmacist sign the prescription. In computerized pharmacies, all such information is printed and stapled to the prescription. Sometimes such information is printed onto labels and the labels affixed right onto the prescription.

When filled by the pharmacist, prescriptions are typically assigned a "prescription number" (often abbreviated "Rx#") that is unique to the pharmacy that filled the prescription. The prescription number is written right on the prescription by the pharmacist. The prescription number has the practical purpose of uniquely identifying the prescription later on while filed (both manual and electronic). The prescription number is also put on the label on the dispensed medication. The patient may be required to reference the prescription number for refills and drug insurance claims. There may also be a legal requirement for prescription numbers for subsequent identification purposes.

As a legal document, some jurisdictions will mandate the archiving of the original paper prescription in the pharmacy. Often the patient cannot take the original prescription with them. Some jurisdictions may entitle patients to a copy. The retention period varies but can be as long as six years. See Exhibit B for sample legislation governing the archiving of prescriptions. Once the retention period has passed, privacy legislation may dictate what can be done with the original paper prescription. Legislation may also dictate what happens to the prescriptions if the pharmacy closes or is sold. For example, if the pharmacy goes out of business, the pharmacist may be required to return the prescription to the patient, to the next closest pharmacy or to the governing body for pharmacists.

Prescriptions for non-narcotic drugs may also be "transferred" from one pharmacy to another for subsequent repeats to be dispensed from another pharmacy. The physical piece of paper that is the prescription is not transferred, but all the information on it is transferred

from one pharmacy to another. Legislation may dictate the protocol by which the transfer occurs and whether the transfer needs to be noted on the original paper prescription.

It is estimated that 3 billion (3 thousand million) prescriptions were written in the United States in 2002. This number has grown from 1.5 billion in 1989 and is expected to continue to grow.

Forgeries, thefts and prevention

Prescriptions are sometimes forged because many narcotics are cheaper and safer as prescription drugs than as street drugs. Forgery takes many forms: Doctor's prescription pads are sometimes stolen, amounts may be altered on legitimate prescriptions, call back numbers may be falsified and phoned or faxed prescriptions faked

Some doctors will use prescription pads that contain similar security measures as checks to make photocopying prescriptions harder. These security measures may be mandated by law - see Exhibit C for sample legal specifications. Legislation may mandate that only certain printers may print prescriptions. New Jersey, for example, requires that only state approved printers may be used to print official "New Jersey Prescription Blanks." (See Exhibit E.) Prescribers can make it harder for amount forgeries by writing out the amounts in words. Again, this may be mandated by law

Some jurisdictions help control stolen prescriptions by requiring special "triplicate prescriptions" for certain classes of drug. Blank triplicates are only available from the regulating agency and are individually numbered. The doctor retains a copy, the second and third copies are given to the patient to give to the pharmacist. The pharmacist retains the second copy and the third copy is submitted to the regulating agency. The regulating agency can issue lists of stolen prescriptions that pharmacists can check. In this example, the prescription's validity is further limited to 72 hours from issuance. This system also has the further benefit of managing "double doctoring" where patients visit multiple doctors to get prescriptions.

States have various laws making theft of prescription blanks or forgery of prescriptions criminal offenses and/or providing special treatment for these offenses (for Example N.J. Stat. 2C:21-1. making forgery of a prescription blank a third degree rather than fourth degree offense)

When forgery is suspected, pharmacists will call the doctor to verify the prescription and will attempt to detain the suspect pending arrival of authorities. Forged prescriptions are no longer considered medical documents and doctor-patient confidentiality rules no longer apply.

Writing prescriptions

Who can write prescriptions

Who can issue prescriptions is governed by local legislation. In the United States, physicians, veterinarians, dentists, and podiatrists have full prescribing power. In all states, optometrists can prescribe medications to treat certain eye diseases, and will also issue

eyeglass prescriptions for corrective eyeglasses. [14] States allow mid-level practitioners different prescription privileges. Nurse practitioners (also known as advance practice nurses), physician assistants, optometrists, homeopathic physicians, naturopathic physicians, some registered pharmacists and doctors of oriental medicine currently represent the spectrum of mid-level practitioners. Each state regulates what (if any) prescription powers members of the above group are allowed. Advance practice nurses and physician assistants have some form of prescriptive authority in 49 states. But registered pharmacists, for example, have limited prescriptive authority in only 6 states..In some states, clinical psychologists (PhD's or PsyD's) who have also undergone specialized training in script-writing may prescribe a limited number of drugs to treat nervous and mental disorders.

Legibility of prescriptions

Prescriptions, when handwritten, are notorious for being often illegible (5% according to an Irish study). Contrary to popular belief, pharmacists do not have special deciphering skills. When in doubt, they call the doctor. At other times, even though some of the individual letters are illegible, the position of the legible letters and length of the word is sufficient to distinguish the medication based on the knowledge of the pharmacist. For doctors that the pharmacist deals with regularly, they learn to read the doctor's handwriting. Patients are advised to ensure that the prescription is legible before leaving the doctor's office. Some jurisdictions have made legible prescriptions a law (e.g. Florida). Some have advocated the elimination of handwritten prescriptions altogether and computer printed prescriptions are becoming increasingly common in some places.

Writing good prescriptions

Independent of the actual prescribing decision, elements of a good prescription writing include:

- careful use of decimal points to avoid ambiguity:
  - avoid unnecessary decimal points: 5 mL instead of 5.0 mL to avoid possible misinterpretation of 5.0=50
  - always zero prefix decimals: e.g. 0.5 instead of .5 to avoid misinterpretation with .5=5
  - never have trailing zeros on decimals: e.g. use 0.5 instead of .50 to avoid misinterpretation with .50=50
  - avoid decimals altogether by changing the units: 0.5 g =500 mg
- "mL" is used instead of "cc" or "cm^3" even though they are technically equivalent
- directions should be written out in full in English although some common Latin abbreviations are listed below
- quantities can be given directly or implied by the frequency & duration of the directions

- where the directions are "as needed" the quantity should always be specified
- where possible, usage directions should specify times (7 am, 3 pm, 11 pm) rather than simply frequency (3 times a day) and especially relationship to meals for orally consumed medication
- use permanent ink
- avoid prn "as needed" - limits & indicators should be specified e.g. "q 3h prn pain"
- for refills - minimum duration between repeats & number of repeats should be specified

Abbreviations

See Appendix 1 for a complete list of common abbreviations found on prescriptions. Many abbreviations are derived from Latin phrases. Hospital pharmacies have more abbreviations, some specific to the hospital. Different jurisdictions follow different conventions on what is abbreviated or not. Prescriptions that don't follow area conventions may be flagged as possible forgeries.

Some abbreviations which are ambiguous, or which in their written form might be confused with something else, are not recommended and should be avoided. These are included in a separate list in Appendix 1.

Non prescription drug prescriptions

Prescriptions are also used for things that are not strictly regulated as a prescription drug. Prescribers will often give non-prescription drugs out as prescriptions because drug benefit plans may reimburse the patient only if the over-the-counter medication is taken under the direction of a doctor. Conversely, if a medication is available over-the-counter, doctors may ask patients if they want it as a prescription and possibly incur a pharmacist's dispensing fee or whether they want to get it themselves at a lower price. If the patient wants the medication not under prescription, the prescriber is usually careful to give the medication name to the patient on a blank piece of paper to avoid any confusion with a prescription. This is applied to non-medications as well. For example, crutches, and registered massage therapy may be reimbursed under some health plans, but only if given out by a prescriber as a prescription.

Prescribers will often use blank prescriptions as general letterhead. A "doctor's note" for absent days from school or work for minor illnesses will often be written on a blank prescription.

Legislation may define certain equipment as "prescription devices". Such prescription devices can only be used under the supervision of authorized personnel and such authorization is typically documented using a prescription. Examples of prescription devices include dental cement (for affixing braces to tooth surfaces), various prothesis, gut sutures, sickle cell tests, cervical cap and ultrasound monitor.

In some jurisdictions, hypodermic syringes are in a special class of its own, regulated as illicit drug use accessories separate from regular medical legislation. Such legislation will often specify a prescription as the mean by which one may legally possess syringes.

Related usage of the term prescription

Prescription may also be used as a short form for prescription drugs to distinguish from over-the-counter drugs. It may also be used in reference to the entire system of controlling drug distribution (as opposed to illicit drugs). "Prescription" is often used as a metaphor for healthy directions from authority. A "green prescription" is direction from a doctor to a patient for exercise and healthy diet.

History

The concept of prescriptions date back to the beginning of history. So long as there were medications and a writing system to capture directions for preparation and usage, there were prescriptions

Modern prescriptions are actually "extemporaneous prescriptions" from the Latin (ex tempore) for "instant". "Extemporaneous" means the prescription is written on the spot for a specific patient with a specific ailment. This is distinguished from the a non-extemporaneous prescription which is a generic recipe for a general ailment. Modern prescriptions evolved with the separation of the role of the pharmacists from that of the physician. Today the term "extemporaneous prescriptions" is reserved for "compound prescriptions" which requires the pharmacist to mix or "compound" the medication in the pharmacy for the specific needs of the patient.

Predating modern legal definitions of a prescription, a prescription traditionally is composed of four parts: a "superscription", "inscription", "subscription" and "signature"

The superscription section contains the date of the prescription and patient information (name, address, age, etc). The symbol "Rx" separates the superscription from the inscriptions sections. In this arrangement of the prescription, the "Rx" is a symbol for recipe or literally "take thou". This is most likely an exhortation to the pharmacist by the doctor, "I want the patient to have the following medication". It should not be interpreted as instructions to the patient to "take thou" as patient instructions are in a later section. Some the literal exhortation to the pharmacist is "take thou this recipe".

The inscription section defines what is the medication. The inscription section is further composed of one or more of

- a "basis" or chief ingredient indended to cure (curare)
- an "adjuvant" to assist its action and make it cure quickly (cito)
- a "corrective" to prevent or lessen any undesirable effect (tuto)
- a "vehicle" or "excipient" to make it suitable for administration and pleasant to the patient (jucunde)

The "subscription" section contains dispensing directions to the pharmacist. This may be compounding instructions or quantities.

The "signature" section contains directions to the patient and is often abbreviated "Sig." or "Signa." It also obviously contains the signature of the prescribing doctor though the word "signature" has two distinct meanings here and the abbreviations are sometimes used to avoid confusion.

Thus sample prescriptions in modern textbooks are often presented as:

Rx: medication *Disp.:* dispensing instructions *Sig.:* patient instructions

Future directions of prescriptions

As a prescription is nothing more than information among a doctor, pharmacist and patient, information technology can be applied to it. Existing information technology is adequate to print out prescriptions. Medical information systems in some hospitals do away with prescriptions within the hospital. There are proposals to securely transmit the prescription from the doctor to the pharmacist using smartcards and the internet. In the UK a project called the Electronic Transfer of Prescriptions (ETP) within the National Programme for IT (NPfIT) is currently piloting such a scheme between doctors and pharmacies.

Within computerized pharmacies, the information on the piece of paper that is the prescription is captured immediately. Thereafter, the prescription is simply an entry within the pharmacy's information system and the paper prescription is stored for legal reasons only.

In cases where a pharmacy is part of a chain of pharmacies, the pharmacies are often linked together through their corporate headquarters with computer technology. Walgreens, for example, uses satellite technology to share patient information. A person who has a prescription filled at one Walgreens can get a refill of that prescription at any other store in the chain, as well as have their information available for new prescriptions at any Walgreens.

Some pharmacies also offer services to customers over the internet. Walgreens' web site, for example, allows customers to order refills for medicine over the internet, and allows them to specify the store that they will pick up the medicine from. Their web site also allows consumers to lookup their prescription history, and to print it out.

Pharmacy information systems are a potential source of valuable information for pharmaceutical companies as it contains information about doctor's prescribing habits. Prescription data mining of such data is a developing, specialized field.

Although computerized information systems offer attractive improvements to paper-based prescriptions, they are not yet available in many prescribers' practices. To reduce prescribing errors, some investigators have developed modified prescription forms that prompt the prescriber to provide all the desired elements of a good prescription. The modified forms also contain pre-defined choices such as common quantities, units and frequencies that the prescriber may circle rather than write out. Such forms are thought to reduce errors (especially omission and handwriting errors) and are actively under evaluation. (See: Kennedy AG, Littenberg B. A Modified Outpatient Prescription Form to Reduce Prescription Errors. Joint Commission Journal of Quality and Safety 2004; 30:480-487.)

Appendix 1: Partial list of abbreviations

This appendix is a list of some abbreviations used in prescriptions. Its listing here does not mean such abbreviations should be used. See main article for discussion on the use of abbreviations. This listing does not include abbreviations for actual pharmaceuticals (which is a separate article in itself). Capitalization and the use of a period is a matter of style. In the attached list, Latin is not capitalized whereas English acronyms are. The period is used wherever there are letters omitted in the abbreviation.

Partial list of prescription abbreviations

Abbreviation (Latin) Meaning

aa (ana) of each

ad (ad) up to

a.c. (ante cibum) before meals

a.d. (aurio dextra) right ear

ad lib. (ad libitum) use as much as one desires; freely

admov. (admove) apply

agit (agita) stir/shake

alt. h. (alternis horis) every other hour

a.m. (ante meridiem) morning, before noon

amp () ampule
amt () amount

aq (aqua) water

a.l., a.s. (aurio laeva, aurio sinister) left ear

A.T.C. () around the clock

a.u. (auris utrae) both ears

bis (bis) twice

b.i.d. (bis in die) twice daily

B.M. () bowel movement

bol. (bolus) as a large single dose (usually intravenously)

B.S. () blood sugar

B.S.A () body surface areas

cap., caps. (capsula) capsule

c (cum) with (usually written with a bar on top of the "c")
To avoid ambiguity, the following abbreviations are not recommended

- *a.u., a.s., a.d.* - Latin for both, left and right ears; the "a" can be misread to be an "o" and interpreted to mean both, right or left eyes
- *d/c* - can mean "discontinue" or "discharge"
- *h.s.* - can mean half strength or "hour of sleep"
- *q.d.* - meant "every day" but the "." after the "q" is interpreted to be an "i" thus "q.i.d." or quadrupling the dose to 4 times a day
- *q.o.d.* - meant "every other day" but the "o" can be interpreted as "." or "i" resulting in double or eight times the frequency
- *SC/SQ* - meant "subcutaneaous" but mistaken for "SL" for "sublingual"
- *T.I.W* - meant 3 times a week but mistaken for twice a week
- *U* - meant "units" but mistaken for "0", "4" or "cc" when poorly written; conversely *cc* can be mistaken for "U"
- *¼g* - meant "microgram" but mistaken for "mg"; this 1000-fold error can cause potentially fatal misunderstandings

Exhibit A: sample legal definition of a prescription

Taken from California's Business and Professions Code Section 4040

4040. (a) "Prescription" means an oral, written, or electronic transmission order that is both of the following: (1) Given individually for the person or persons for whom ordered that includes all of the following:
(A) The name or names and address of the patient or patients.
(B) The name and quantity of the drug or device prescribed and the directions for use.
(C) The date of issue.
(D) Either rubber stamped, typed, or printed by hand or typeset, the name, address, and telephone number of the prescriber, his or her license classification, and his or her federal registry number, if a controlled substance is prescribed.
(E) A legible, clear notice of the condition for which the drug is being prescribed, if requested by the patient or patients.
(F) If in writing, signed by the prescriber issuing the order, or the certified nurse-midwife, nurse practitioner, or physician assistant who issues a drug order pursuant to Section 2746.51,2836.1, or 3502.1.

(2) Issued by a physician, dentist, optometrist, podiatrist, or veterinarian or, if a drug order is issued pursuant to Section 2746.51, 2836.1, or 3502.1, by a certified nurse-midwife, nurse practitioner, or physician assistant licensed in this state.
(b) Notwithstanding subdivision (a), a written order of the prescriber for a dangerous drug, except for any Schedule II controlled substance, that contains at least the name and signature of the prescriber, the name and address of the patient in a manner consistent with paragraph (3) of subdivision (b) of Section 11164 of the Health and Safety Code, the name and quantity of the drug prescribed, directions for use, and the date of issue may be treated as a prescription by the dispensing pharmacist as long as any additional information required by subdivision (a) is readily retrievable in the pharmacy. In the event of a conflict between this subdivision and Section 11164 of the Health and Safety Code, Section 11164 of the Health and Safety Code shall prevail.
(c) "Electronic transmission prescription" includes both image and data prescriptions. "Electronic image transmission prescription" means any prescription order for which a facsimile of the order is received by a pharmacy from a licensed prescriber. "Electronic data transmission prescription" means any prescription order, other than an electronic image transmission prescription, that is electronically transmitted from a licensed prescriber to a pharmacy.
(d) The use of commonly used abbreviations shall not invalidate an otherwise valid prescription.
(e) Nothing in the amendments made to this section (formerly Section 4036) at the 1969 Regular Session of the Legislature shall be construed as expanding or limiting the right that a chiropractor, while acting within the scope of his or her license, may have to prescribe a device.

Exhibit B: sample legal requirement for storage of prescriptions

From the Mississippi Board of Pharmacy

ARTICLE XIII PRESCRIPTIONS TO BE FILED
1. All prescriptions shall be filed in one of the following ways:
A. Three separate files may be maintained; a file for Schedule II prescriptions dispensed; a file for Schedule III, IV and V prescriptions dispensed; and a file for all other prescriptions dispensed.
B. Two files may be maintained; a file for all Schedule II prescriptions dispensed and another file for all other prescriptions dispensed, including those in Schedule III, IV and V. If this method is used, the prescriptions for Schedule III, IV and V substances must be stamped with the letter "C" in red ink, not less than one inch high, in the lower right-hand corner. This distinctive marking makes the records readily retrievable for inspection. Pharmacies with automatic data processing systems are exempted from marking Schedule III, IV and V controlled substance prescriptions with the red "C".
2. A hard copy of original prescriptions, whether records are maintained manually or in a data processing system, shall be assigned a serial number and maintained by the pharmacy in numerical and chronological order. All prescriptions shall be maintained for at least five years from the date of original dispensing.

3. If a pharmacy utilizes a data processing system for record keeping, all computer generated labels should be affixed to the prescription document in such a manner as not to obscure information on the face of the document.

Exhibit C: sample legal requirements for security and format

From Indiana Board of Pharmacy

856 IAC 1-34-2 Security feature requirements
Authority: IC 35-48-7-8
Affected: IC 16-42-19-5

Sec. 2. (a) All controlled substance prescriptions written by licensed Indiana practitioners, as defined by IC 16-42-19-5, must contain the following security features: (1) A latent, repetitive "void" pattern screened at five percent (5%) in reflex blue must appear across the entire face of the document when the prescription is photocopied. (2) There shall be a custom artificial watermark printed on the back side of the base paper so that it may only be seen at a forty-five (45) degree angle. The watermark shall consist of the words "Indiana Security Prescription", appearing horizontally in a step-and-repeated format in five (5) lines on the back of the document using 12-point Helvetica bold type style. (3) An opaque RX symbol must appear in the upper right-hand corner, one-eighth (c) of an inch from the top of the pad and five-sixteenths (5 /16) of an inch from the right side of the pad. The symbol must be three-fourths (3/4) inch in size and must disappear if the prescription copy is lightened. (4) Six (6) quantity check-off boxes must be printed on the form and the following quantities must appear and the appropriate box be checked off for the prescription to be valid: (A) 1-24 (B) 25-49 (C) 50-74 (D) 75-100 (E) 101-150 (F) 151 and over. (5) No advertisements may appear on the front or back of the prescription blank. (6) Logos, defined as a symbol utilized by an individual, professional practice, professional association, or hospital, may appear on the prescription blank. The upper left one (1) inch square of the prescription blank is reserved for the purpose of logos. Only logos, as defined by this subdivision, may appear on the prescription blank. (7) Only one (1) prescription may be written per prescription blank. The following statement must be printed on the bottom of the pad: "Prescription is void if more than one (1) prescription is written per blank.". (8) Refill options that can be circled by the prescriber must appear below any logos and above the signature lines on the left side of the prescription blank in the following order: Refill NR 1 2 3 4 5 Void after_____. (9) Practitioner name and state issued professional license number must be preprinted, stamped, or manually printed on the prescription. (10) All prescription blanks printed under this rule shall be four and one-fourth (4-1/4) inches high and five and one-half (5-1/2) inches wide. (b) Nothing in this rule shall prevent licensed Indiana practitioners from utilizing security paper prescriptions for the prescribing of any legend drug. (Indiana Board of Pharmacy; 856 IAC 1-34-2; filed Jul 5, 1995, 9:45 a.m.: 18 IR 2782, eff Jan 1, 1996)

Exhibit D: sample requirements on information added by the pharmacist

Taken from the Ontario's Drug and Pharmacies Regulation Act, paragraph 156.

(1) Every person who dispenses a drug pursuant to a prescription shall ensure that the following information is recorded on the prescription, (a) the name and address of the

person for whom the drug is prescribed; (b) the name, strength (where applicable) and quantity of the prescribed drug; (c) the directions for use, as prescribed; (d) the name and address of the prescriber; (e) the identity of the manufacturer of the drug dispensed; (f) an identification number or other designation; (g) the signature of the person dispensing the drug and, where different, also the signature of the person receiving a verbal prescription; (h) the date on which the drug is dispensed; (i) the price charged. R.S.O. 1990, c. H.4, s. 156 (1).

Exhibit E: New Jersey requirements for prescription blanks

From New Jersey official statutes

45:14-55 Use of New Jersey Prescription Blanks. 16. a. A practitioner practicing in this State shall use non-reproducible, non-erasable safety paper New Jersey Prescription Blanks bearing that practitioner's license number whenever the practitioner issues prescriptions for controlled dangerous substances, prescription legend drugs or other prescription items. The prescription blanks shall be secured from a vendor approved by the Division of Consumer Affairs in the Department of Law and Public Safety. b. A licensed practitioner practicing in this State shall maintain a record of the receipt of New Jersey Prescription Blanks. The practitioner shall notify the Office of Drug Control in the Division of Consumer Affairs as soon as possible but no later than 72 hours of being made aware that any New Jersey Prescription Blank in the practitioner's possession has been stolen. Upon receipt of notification, the Office of Drug Control shall take appropriate action, including notification to the Department of Human Services and the Attorney General. 45:14-56 Health care facility prescriptions. 17. a. Prescriptions issued by a health care facility licensed pursuant to P.L.1971, c.136 (C.26:2H-1 et seq.) shall be written on non-reproducible, non-erasable safety paper New Jersey Prescription Blanks. The prescription blanks shall be secured from a vendor approved by the Division of Consumer Affairs in the Department of Law and Public Safety. The New Jersey Prescription Blanks shall bear the unique provider number assigned to that health care facility for the issuing of prescriptions for controlled dangerous substances, prescription legend drugs or other prescription items. b. A health care facility shall maintain a record of the receipt of New Jersey Prescription Blanks. The health care facility shall notify the Office of Drug Control in the Division of Consumer Affairs as soon as possible but no later than 72 hours of being made aware that any New Jersey Prescription Blank in the facility's possession has been stolen. Upon receipt of notification, the Office of Drug Control shall take appropriate action including notification to the Department of Human Services and the Attorney General. 45:14-57 Requirements for prescription to be filled. 18.A prescription issued by a practitioner or health care facility licensed in New Jersey shall not be filled by a pharmacist unless the prescription is issued on a New Jersey Prescription Blank bearing the practitioner's license number or the unique provider number assigned to a health care facility. 45:14-59 Format for New Jersey Prescription Blanks. 20.The Division of Consumer Affairs in the Department of Law and Public Safety shall establish the format for uniform, non-reproducible, non-erasable safety paper prescription blanks, to be known as New Jersey Prescription Blanks, which format shall include an identifiable logo or symbol that will appear on all prescription blanks. The division shall

approve a sufficient number of vendors to ensure production of an adequate supply of New Jersey Prescription Blanks for practitioners and health care facilities statewide.

See also

- Prescription drugs

Medication

A *medication* is a licenced drug taken to cure or reduce symptoms of an illness or medical condition. Medications are generally divided into two groups by the United States and similar laws -- Over-the-counter drug (OTC) medications, which are available in pharmacies and supermarkets without special restrictions, and Prescription only medicines (POM), which must be prescribed by a physician, physician assistant, nurse practitioner, or dentist. The International Narcotics Control Board of the United Nations imposes a world law of prohibition or censorship of certain medications. They publish a lengthy list of chemicals and plants whose trade and consumption (where applicable) is forbidden. Most OTC medication is generally considered to be safe enough that most persons will not hurt themselves accidentally by taking it as instructed. Many countries, such as the UK have a third category of pharmacy medicines which can only be sold in registered pharmacies, by or under the supervision of a pharmacist. However, the precise distinction between OTC and prescription depends on the legal jurisdiction. Medications are typically produced by pharmaceutical companies and are often patented. Those that are not patented are called generic drugs.

Classification

Medication can be usually classified in various ways, e.g. by its chemical properties, mode of administration, or biological system affected. An elaborate and widely used classification system is the Anatomical Therapeutic Chemical Classification System.

Types of medication

For the gastrointestinal tract or digestive system

- Upper digestive tract: antacids, reflux suppressants, antiflatulents, antidopaminergics, proton pump inhibitors, H2-receptor antagonists, cytoprotectants, prostaglandin analogues
- Lower digestive tract: laxatives, antispasmodics, antidiarrhoeals, bile acid sequestrants, opioids

For the cardiovascular system

- General: beta-receptor blocker, calcium channel blockers, diuretics, cardiac glycosides, antiarrhythmics, nitrate, antianginals, vasoconstrictor, vasodilator, peripheral activator

- **Affecting** Blood pressure**:** ACE inhibitors**,** angiotensin receptor blockers**,** alpha blocker

- Coagulation: anticoagulant, heparin, antiplatelet drug, fibrinolytic, anti-hemophilic factor, haemostatic drugs
- Atherosclerosis/cholesterol agents: hypolipidaemic agents, statins.

For the central nervous system

See also: Psychoactive drug

hypnotic, **anaesthetics**, **antipsychotic**, **antidepressant** (including tricyclic antidepressants, **monoamine oxidase inhibitor**, lithium salt, **selective serotonin reuptake inhibitor**), **anti-emetic**, **anticonvulsant** and antiepileptic, **anxiolytic**, **barbiturate**, movement disorder drug, **stimulant** (including Amphetamine), **benzodiazepine**, cyclopyrrolone, dopamine antagonist, **antihistamine**, cholinergic, **anticholinergic**, emetic, **cannabinoids**, 5-HT antagonist

For pain & consciousness (analgesic drugs)

Further information: Analgesic

The main classes of painkillers are NSAIDs, opioids and various orphans such as paracetamol, tricyclic antidepressants and anticonvulsants.

For musculo-skeletal disorders

NSAIDs (including COX-2 selective inhibitors), muscle relaxant, neuromuscular drug anticholinesterase

For the eye

- General: adrenergic neurone blocker, astringent, ocular lubricant
- Diagnostic: topical anesthetics, sympathomimetics, parasympatholytics, mydriatics, cycloplegics
- Anti-bacterial: antibiotics, topical antibiotics, sulfa drugs, aminoglycosides, fluoroquinolones
- Anti-viral:
- Anti-fungal: imidazoles, polyenes
- Anti-inflammatory: NSAIDs, corticosteroids

- Anti-allergy: mast cell inhibitors
- Anti-glaucoma: adrenergic agonists, beta-blockers, carbonic anhydrase inhibitors/hyperosmotics, cholinergics, miotics, parasympathomimetics, prostaglandin agonists/prostaglandin inhibitors. nitroglycerin

For the ear, nose and oropharynx

sympathomimetic, **antihistamine**, **anticholinergic**, NSAIDs, steroid, **antiseptic**, **local anesthetic**, **antifungal**, cerumenolytic

For the respiratory system

bronchodilator, NSAIDs, anti-allergic, antitussive, mucolytic, decongestant corticosteroid, beta-receptor antagonist, anticholinergic, steroid

For endocrine problems

androgen, antiandrogen, gonadotropin, corticosteroid, growth hormone, insulin, antidiabetic (sulfonylurea, biguanide/metformin, thiazolidinedione, insulin), thyroid hormones, antithyroid drugs, calcitonin, diphosponate, vasopressin analogues

For the reproductive system or urinary system

antifungal, alkalising agent, quinolones, antibiotic, cholinergic, anticholinergic, anticholinesterase, antispasmodic, 5-alpha reductase inhibitor, selective alpha-1 blocker, sildenafil

For contraception

contraceptive, oral contraceptives, spermicide, depot contraceptives

For obstetrics and gynaecology

NSAIDs, anticholinergic, haemostatic drug, antifibrinolytic, Hormone Replacement Therapy, bone regulator, beta-receptor agonist, follicle stimulating hormone, luteinising hormone, LHRH gamolenic acid, gonadotropin release inhibitor, progestogen, dopamine agonist, oestrogen, prostaglandin, gonadorelin, clomiphene, Tamoxifen, Diethylstilbestrol

For the skin

emollient, anti-pruritic, antifungal, disinfectant, scabicide, pediculicide, tar products, vitamin A derivatives, vitamin D analogue, keratolytic, abrasive, systemic antibiotic, topical

antibiotic, hormones, desloughing agent, exudate absorbent, fibrinolytic, proteolytic, sunscreen, antiperspirant, corticosteroid

For infections and infestations

antibiotic, antifungal, antileprotic, antituberculous drug, antimalarial, anthelmintic, amoebicide, antiviral, antiprotozoal, antiserum

For immunology

vaccine, immunoglobulin, immunosuppressant, interferon, monoclonal antibody

For allergic disorders

anti-allergic, antihistamine, NSAIDs

For nutrition

tonic, iron preparation, electrolyte, parenteral nutritional supplement, vitamins, anti-obesity drug, anabolic drug, haematopoietic drug, food product drug

For neoplastic disorders

cytotoxic drug, sex hormones, aromatase inhibitor, somatostatin inhibitor, recombinant interleukins, G-CSF, erythropoietin

For diagnostics

contrast media

For euthanasia

A euthanaticum is used for euthanasia and physician-assisted suicide, see also barbiturates.

Other/related topics

Polypharmacy: suggests that multiple use of prescribed and non-prescribed medications, (use of 5 or more), can have adverse effects on the recipient.

Zoopharmacognosy: Animal usage of drugs and non-foods.

See also

- Herbalism
- Medicine
- Pharmacology
- Pharmaceutical company
- Vaccine

Phosphate binders

Phosphate binders are a group of medications used to reduce the absorption of phosphate and taken with meals and snacks. They are typically used in patients with chronic renal failure (CRF) as they cannot get rid of the phosphate that gets into their blood (i.e. the serum phosphate in chronic renal failure is typically elevated).

Clinical use

For patients with chronic renal failure, controlling serum phosphate is important because it is associated with bone pathology and regulated together with serum calcium by the parathyroid hormone (PTH). High (serum) phosphate levels (known as hyperphosphatemia) normally results in an elevation of the PTH level, which then leads to more phosphate excretion into the urine.[1] If the kidneys do not function properly the phosphate level increases. Also, the serum calcium levels tend to be low. This is because the kidneys in chronic renal failure do not produce the active form of vitamin D (1,25-dihydroxycholecalciferol), which is important for calcium absorption from food. Low serum calcium levels, like high phosphate, also lead to a high PTH.

A high PTH leads to a large mobilization of calcium from the bone and, if it is not replaced, bone is lost. Bone loss and damage due to CRF is called renal osteodystrophy. To avoid a high PTH and bone loss in patients with CRF, CRF patients typically avoid high phosphate intake and take calcium supplements, vitamin D and phosphate binders.

Mechanism of action

These agents work by binding to phosphate in the GI tract, thereby making it unavailable to the body for absorption. Hence, these drugs are usually taken with meals to bind any phosphate that may be present in the ingested food. Phosphate binders may be simple molecular entities (such as aluminum, calcium, or lanthanum salts) that react with phosphate and form an insoluble compound. Phosphate binders, such as sevelamer, may also be polymeric structures which bind to phosphate and are then excreted.

Adverse effects

With regard to phosphate binders, aluminum-containing compounds (such as aluminum hydroxide) are the least preferred because prolonged aluminum intake can cause encephalopathy and osteomalacia. If calcium is already being used as a supplement, additional calcium used as a phosphate binder may cause hypercalcemia and tissue-damaging calcinosis. One may avoid these adverse effects by using phosphate binders that do not contain calcium or aluminum as active ingredients, such as lanthanum carbonate or sevelamer.

Common phosphate binders

- Aluminum hydroxide (Alucaps®)
- Calcium carbonate (Calcichew®, Titralac®)
- Calcium acetate (Phosex®) Lanthanum carbonate (Fosrenol®) Sevelamer (Renagel®)

Reference

1. ʻ Lederer E, Ouseph R, Erbeck K. Hyperphosphatemia, eMedicine.com, URL: http://www.emedicine.com/med/topic1097.htm, Accessed on July 14, 2005.

Calcium carbonate

Systematic name Calcium carbonate

Other names Limestone, calcite, aragonite, chalk, marble

Molecular formula $CaCO_3$

Molar mass 100.087 g/mol

Appearance White powder.
CAS number [471-34-1]

Properties

Density and phase 2.83 g/cm^3, solid.

Solubility in water Insoluble

Melting point 825°C (1098 K)

Boiling point Decomposes

Thermochemistry

”$_f$H$^0_{liquid}$ -1154 kJ/mol

”$_f$H$^0_{solid}$ -1207 kJ/mol
S$^0_{solid}$ 93 J/mol·K

Structure

Molecular shape Linear

Coordination geometry Tetrahedral

Hazards

MSDS External MSDS

Main hazards Not hazardous.

NFPA 704

Flash point

Non-flammable.

R/S statement R: R36, R37, R38, S: S26, S36

Supplementary data page

Structure and properties n, μ*r*, etc.

Thermodynamic data

Phase behaviour Solid, liquid, gas

Related compounds

Other anions Calcium bicarbonate, Calcium sulfate

Other cations Magnesium carbonate (dolomite), Strontium carbonate

Related compounds Calcium oxide

Except where noted otherwise, data are given for materials in their standard state (at 25°C, 100 kPa)

Calcium carbonate is a chemical compound, with chemical formula $CaCO_3$. It is commonly used medicinally as a calcium supplement or as an antacid. Calcium carbonate is the active ingredient in agricultural lime. It is a common substance found as rock in all parts of the world and is the main component of seashells and the shell of snails. It is usually the principal cause of hard water.

Occurrence

Calcium carbonate is found naturally as the following minerals and rocks:

- Aragonite
- Calcite
- Chalk
- Limestone
- Marble
- Travertine

Eggshells are composed of approximately 95% calcium carbonate.

To test whether a mineral or rock contains calcium carbonate, strong acids, like hydrochloric acid, can be dropped with a dropper onto it. If it does contain the chemical, it will fizz and produce carbon dioxide; otherwise, it probably wouldn't react vigorously. For example, all of the rocks/mineral mentioned above will react with acid.

Preparation

The vast majority of calcium carbonate used in industry is extracted by mining or quarrying. Pure calcium carbonate (e.g. for food or pharmaceutical use), can be produced from a pure quarried source (usually marble) or it can be prepared by passing carbon dioxide into a solution of calcium hydroxide: the calcium carbonate precipitates out, and this grade of product is referred to as a precipitate (abbreviated to PCC).

$Ca(OH)_2 + CO_2 \rightarrow CaCO_3 + H_2O$

Chemical properties

Calcium carbonate shares the typical properties of other carbonates. Notably:

1. it reacts with strong acids, releasing carbon dioxide:
   $CaCO_3 + 2HCl \rightarrow CaCl_2 + CO_2 + H_2O$
2. it releases carbon dioxide on heating (to above 825 °C in the case of $CaCO_3$), to form calcium oxide, commonly called burnt lime:
   $CaCO_3 \rightarrow CaO + CO_2$

Calcium carbonate will react with water that is saturated with carbon dioxide to form the soluble calcium bicarbonate.

$CaCO_3 + CO_2 + H_2O \rightarrow Ca(HCO_3)_2$

This reaction is important in the erosion of carbonate rocks, forming caverns, and leads to hard water in many regions.

Uses

The main use of calcium carbonate is in the construction industry, either as a building material in its own right (e.g. marble) or limestone aggregate for roadbuilding or as an ingredient of cement or as the starting material for the preparation of builder's lime by burning in a kiln . A common contaminate is magnesium carbonate.

Calcium carbonate is widely used as an extender in paints, in particular matte emulsion paint where typically 30% by weight of the paint is either chalk or marble.

Calcium carbonate is also widely used as a filler in plastics. Some typical examples include around 15 to 20% loading of chalk in uPVC drain pipe, 5 to 15% loading of stearate coated chalk or marble in uPVC window profile. Fine ground calcium carbonate is an essential ingredient in the microporous film used in babies nappies and some building films as the pores are nucleated around the calcium carbonate particles during the manufacture of the film by biaxial stretching.

Calcium carbonate is also used in a wide range of trade and DIY adhesives, sealants and decorating fillers. Ceramic tile adhesives typically contain 70 to 80% limestone. Decorating crack fillers contain similar levels of marble or dolomite. It is also mixed with putty in setting Stained glass windows, and as a resist to prevent glass from sticking to kiln shelves when firing glazes and paints at high temperature.

Calcium carbonate is widely used medicinally as an inexpensive dietary calcium supplement,[1] antacid, and/or phosphate binder. It is also used in the pharmaceutical industry as a base material for tablets of other pharmaceuticals.

Calcium carbonate is known as whiting in ceramics/glazing applications, where it is used as a common ingredient for many glazes in its white powdered form. When a glaze containing this material is fired in a kiln, the whiting acts as a flux material in the glaze.

It is commonly called chalk as it has been a major component of blackboard chalk. Chalk may consist of either calcium carbonate or gypsum, hydrated calcium sulfate $CaSO_4 \cdot 2H_2O$.

In North America, calcium carbonate has begun to replace kaolin in the production of glossy paper. Europe has been practicing this as alkaline papermaking or acid-free papermaking for some decades. Carbonates are available in forms: ground calcium carbonate (GCC) or precipitated calcium carbonate (PCC). The latter has a very fine and controlled particle size, on the order of 2 micron in diameter, useful in coatings for paper.

As a food additive, it is used in some soy milk products as a source of dietary calcium.

In 1989, Dr. Simmons introduced $CaCO_3$ into the Whetstone Brook in Massachusetts. His hope was that the calcium carbonate would counter the acid in the stream from acid rain and save the trout that had ceased to spawn. Although his experiment was a success, it did increase the amounts of aluminum ions in the area of the brook that was not treated with the limestone. This shows that $CaCO_3$ can be added to neutralize the effects of acid rain in river ecosystems. Nowadays, calcium carbonate is used to neutralise acidic conditions in both soil and water.

Calcination Equilibrium

Equilibrium Pressure of CO_2 over $CaCO_3$	
550 °C	0.055 kPa
587 °C	0.13 kPa
605 °C	0.31 kPa
680 °C	1.80 kPa
727 °C	5.9 kPa
748 °C	9.3 kPa
777 °C	14 kPa
800 °C	24 kPa
830 °C	34 kPa
852 °C	51 kPa
871 °C	72 kPa
881 °C	80 kPa
891 °C	91 kPa
898 °C	101 kPa
937 °C	179 kPa
1082 °C	901 kPa
1241 °C	3961 kPa

Calcination of limestone using charcoal fires to produce quicklime has been practiced since antiquity by cultures all over the world. The answer to the question, "how hot does the fire have to be?" is usually given as 825 °C, but stating an absolute threshold is misleading. Calcium carbonate exists in equilibrium with calcium oxide and carbon dioxide at any temperature. At each temperature there is a partial pressure of carbon dioxide that is in equilibrium with calcium carbonate. At room temperature the equilibrium overwhelmingly favors calcium carbonate, because the equilibrium CO***2*** pressure is only a tiny fraction of the partial CO***2*** pressure in air, which is about 0.035 kPa. At temperatures above 550 °C the equilibrium CO2 pressure begins to exceed the CO2 pressure in air. So above 550 °C, calcium

carbonate begins to outgas CO2 into air. But in a charcoal fired kiln, the concentration of CO2 will be much higher than it is in air. Indeed if all the oxygen in the kiln is consumed in the fire, then the partial pressure of CO2 in the kiln can be as high as 20 kPa. The table shows that this equilibrium pressure is not achieved until the temperature is nearly 800 °C. For the outgassing of CO2 from calcium carbonate to happen at an economically useful rate, the equilibrium pressure must significantly exceed the ambient pressure of CO2. And for it to happen rapidly, the equilibrium pressure must exceed total atmospheric pressure of 101 kPa, which happens at 898 °C.

Solubility of calcium carbonate in water

Calcium carbonate is poorly soluble in water.

Calcium Ion Solubility as a function of CO_2 partial pressure at 25 °C		
P_{CO2} (atm)	pH	$[Ca^{2+}]$ (mol/L)
10^{-12}	12.0	5.19×10^{-3}
10^{-10}	11.3	1.12×10^{-3}
10^{-8}	10.7	2.55×10^{-4}
10^{-6}	9.83	1.20×10^{-4}
10^{-4}	8.62	3.16×10^{-4}
3.5×10^{-4}	**8.27**	**4.70×10^{-4}**
10^{-3}	7.96	6.62×10^{-4}
10^{-2}	7.30	1.42×10^{-3}
10^{-1}	6.63	3.05×10^{-3}
1	5.96	6.58×10^{-3}
10	5.30	1.42×10^{-2}

The table on the right shows the result for [Ca^{2+}] and [H^{+}] (in the form of pH) as a function of ambient partial pressure of CO_2. At atmospheric levels of ambient CO_2 the table indicates the solution will be slightly alkaline. The trends the table shows are

1) As ambient CO_2 partial pressure is reduced below atmospheric levels, the solution becomes more and more alkaline. At extremly low P_{CO_2}, dissolved CO_2, bicarbonate ion, and carbonate ion largely evaporate from the solution, leaving a highly alkaline solution of calcium hydroxide, which is more soluble than $CaCO_3$. 2) As ambient CO_2 partial pressure increases to levels above atmospheric, pH drops, and much of the carbonate ion is converted to bicarbonate ion, which results in higher solubility of Ca^{2+}.

The effect of the latter is especially evident in day to day life of people who have hard water. Water in aquifers underground can be exposed to levels of CO2 much higher than atmospheric. As such water percolates through calcium carbonate rock, the CaCO3 dissolves according to the second trend. When that same water then water emerges from the tap, in time it comes into equilibrium with CO2 levels in the air by outgassing its excess CO2. The calcium carbonate becomes less soluble as a result and the excess precipitates as lime scale. This same process is responsible for the formation of stalactites and stalagmites in limestone caves.

References

1. ^ CALTRO
2. ^ CSUDH
3. ^ CRC Handbook of Chemistry and Physics, 44th ed.

Psychoactive drugs

A *psychoactive drug* or *psychotropic substance* is a chemical substance that acts primarily upon the central nervous system where it alters brain function, resulting in temporary changes in perception, mood, consciousness and behavior.

These drugs may be used recreationally to purposefully alter one's consciousness (such as coffee, alcohol or cannabis), as entheogens for spiritual purposes (such as the mescaline-containing peyote cactus or psilocybin-containing mushrooms), and also as medication (such as the use of narcotics in controlling pain, stimulants to treat narcolepsy and attention disorders, as well as anti-depressants and anti-psychotics for treating neurological and psychiatric illnesses).

Many of these substances (especially the stimulants and depressants) can be habit-forming, causing chemical dependency and may lead to substance abuse. Conversely, others (namely the psychedelics) can help to treat and even cure such addictions.

A brief history of drug use

Drug use is not a new phenomenon by any means. There is archaeological evidence of the use of psychoactive substances dating back at least 10,000 years, and historical evidence of cultural use over the past 5,000 years.[4]

While medicinal use plays a very large role, it has been suggested that the urge to alter one's consciousness is as primary as the drive to satiate thirst, hunger or sexual desire.[5]

Some may point a finger to marketing, availability or the pressures of modern life as to why humans use so many psychoactives in their daily lives, but one only has to look back at history, or even to children with their desire for spinning, swinging, sliding amongst other activities to see that the drive to alter one's state of mind is universal.[6]

This relationship is not limited to humans. A surprising number of animals consume different psychoactive plants and animals, berries and even fermented fruit, clearly becoming intoxicated. Traditional legends of sacred plants often contain references to animals that introduced humankind to their use.[7]

Biology suggests an evolutionary connection between psychoactive plants and animals, as to why these chemicals and their receptors exist within the nervous system.[8]

The 20th century has seen governments initially responding to many drugs by banning them and making their use, supply or trade a criminal offence. During the Prohibition era in America, alcohol had this approach used for 13-ish years. However, globalization has made many governments realize that the use of illicit drugs can no longer truly be eradicated. In many countries, there has been a move toward harm reduction by health services, where the use of illicit drugs is neither condoned nor promoted, but services and support are provided to ensure users have the negative effects of their illicit drug use minimised. This often goes hand-in-hand with supply reduction strategies by law enforcement agencies.

Other psychoactive drugs

- Aphrodisiacs
  - Bremelanotide
- In a broader sense also:
  - Antiemetics
  - Analgesics
  - Antiepileptics

Ways psychoactive drugs affect the brain

There are many ways in which psychoactive drugs can affect the brain. While some drugs affect neurons presynaptically, others act postsynaptically and some drugs don't even affect the synapse, working on neural axons instead. Here is a general breakdown of the ways psychoactive drugs can work.

1. Prevent The Action Potential From Starting
   - Lidocaine, TTX (they bind to voltage-gated sodium channels, so no action potential begins even when a generator potential passes threshold)
2. Neurotransmitter Synthesis
   - Increase - L-Dopa, tryptophan, choline (precursors)
   - Decrease - PCPA (inhibits synthesis of 5HT)
   - Causes increased sensitivity to the five senses, due to an increasing number of signals being sent to the brain.
3. Neurotransmitter Packaging
   - Increase - MAO Inhibitors
   - Decrease - Reserpine (pokes holes in the synaptic vesicles of catecholamines)
4. Neurotransmitter Release
   - Increase - Black Widow Spider venom (ACh)
   - Decrease - Botulinum Toxin (ACh), Tetanus (GABA)
5. Agonists - Mimic the original neurotransmitters and activate the receptors
   - Muscarine, Nicotine **(ACh)**
   - AMDA, NMDA (Glu)
   - Alcohol, Benzodiazepines (GABA)
6. Antagonists - Bind to the receptor sites and block activation
   - Atropine, Curare **(ACh)**
   - PCP (Glu)

- Caffeine **(**adenosine**)**

7. Prevent ACh Breakdown

- Insecticides**, Nerve Gas**

8. Prevent Reuptake

- Cocaine **(**DA**),**
    - Tricyclics, SSRIs (5-HT, NE)

- based on information taught in NSC 201, Vanderbilt University

Philosophy and morality of psychoactive drugs

For thousands of years, people have studied psychoactive drugs, both by observation and ingestion. However, humanity remains bitterly divided regarding psychoactive drugs, and their value and use has long been an issue of major philosophical and moral contention, even to the point of war (the Opium Wars being a prime example of a war being fought over psychoactives). A majority of youths and adults consume one or more psychoactive drugs. In the West, the most common by numbers of users are caffeine, alcohol, and nicotine, in that order. Most people accept restrictions on some and the prohibition of others, especially the "hard" drugs, which are generally illegal in most countries.[9][10][11]

Because so many consumers want to reduce or eliminate their own use[12], many professionals, self-help groups, and businesses specialize in that field, with varying degrees of success. Many parents attempt to influence the actions and choices of their children regarding psychoactives.

Debate continues over whether each psychoactive drug being considered is or is not spiritual, sinful, therapeutic, poisonous, ethical, immoral, effective, risky, responsible, recreational, a weapon to use against enemies, a boost to the economy, etc. These attitudes can often be deeply rooted in philosophical and/or religious beliefs, making it difficult to reach consensus or agreement on the proper moral and philosophical stance regarding psychoactive drugs. A major point of contention regards the role of government, whether it should, with respect to each drug, remain neutral, make use safer, educate for abstention, educate for moderation, regulate trade, require a prescription, restrict promotion, prohibit altogether, alter penalties, change enforcement, and so on.

See also

- Antipsychotics
- Hallucinogens
- Medication

- Stimulants

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- (Note: new ISBN for Intoxication comes in January 2007 and is 978-1-59477-069-2)

Alkyl nitrites

Alkyl nitrites are compounds of structure R-ONO. Formally they are alkyl esters of nitrous acid.

The first few members of the series are volatile liquids; methyl and ethyl nitrite are gaseous at room temperature and pressure. The compounds have a distinctive fruity odor.

Preparation and use

Organic nitrites are prepared from alcohols and sodium nitrite in sulfuric acid solution. They decompose slowly on standing, the decomposition products being oxides of nitrogen, water, the alcohol, and polymerization products of the aldehyde.[1]

In the laboratory, solutions of alkyl nitrites in glacial acetic acid are sometimes used as mild nitrating agents. The nitrating species is acetyl nitrate generated in situ.

Antidepressants

An *antidepressant* is a medication designed to treat or alleviate the symptoms of clinical depression. Some antidepressants, notably the tricyclics, are commonly used off-label in the treatment of neuropathic pain, whether or not the patient is depressed. Smaller doses are generally used for this purpose, and they often take effect more quickly. Many antidepressants also are used for the treatment of anxiety disorders, and tricyclic antidepressants are used in the treatment of chronic pain disorders such as chronic functional abdominal pain (CFAP), myofascial pain syndrome, and post-herpetic neuralgia.

The main classes of antidepressants have similar efficacy, but the newer types are generally regarded to have a more benign side-effect profile and less risk of lethality if taken in overdose.

History

Like many psychiatric drugs, antidepressants were discovered by accident. The first useful antidepressants belonged to a group called MAOIs (*M*ono*A*mine *O*xidase *I*nhibitors) and were discovered in the early 1950s. The original member of this group was iproniazid, which was originally developed to treat tuberculosis.[1] The next group were the tricyclic antidepressants. The first was imipramine. They were effective and safer than the MAOI but still quite dangerous in overdose. They are still used today but have been largely replaced by another group: SSRIs (*S*elective *S*erotonin *R*euptake *I*nhibitors). The first SSRI was Zimelidine. Drugs from all three groups have been found to improve the mood of depressed patients. The SSRI antidepressants were early examples of rational drug design.

Classes and members

Antidepressants (*ATC N06A*):

Monoamine oxidase inhibitors (MAOI) - Harmaline, Iproclozide, Iproniazid, Isocarboxazid, Nialamide, Phenelzine, Selegiline, Toloxatone, Tranylcypromine

Reversible inhibitor of monoamine oxidase A (RIMA) - Brofaromine, Moclobemide

Dopamine reuptake inhibitor (DARI) - Amineptine, Phenmetrazine, Vanoxerine, Modafinil

Norepinephrine-dopamine reuptake inhibitors - Bupropion

Norepinephrine reuptake inhibitor (NRI) or (NARI) - Atomoxetine, Maprotiline, Reboxetine, Viloxazine

Serotonin-norepinephrine reuptake inhibitor (SNRI) - Duloxetine, Milnacipran, Venlafaxine

Selective serotonin reuptake inhibitor (SSRI) - Alaproclate, Etoperidone, Citalopram, Escitalopram, Fluoxetine, Fluvoxamine, Paroxetine,

Selective serotonin reuptake enhancer (SSRE) - Tianeptine

Tricyclic antidepressants (TCA) - Amitriptyline, Amoxapine, Butriptyline, Clomipramine, Desipramine, Dibenzepin, Dothiepin, Doxepin, Imipramine, Iprindole, Lofepramine, Melitracen, Nortriptyline, Opipramol, Protriptyline, Trimipramine

Tetracyclic antidepressants - Maprotiline, Mianserin, Nefazodone, Trazodone

Noradrenergic and specific serotonergic antidepressant (NaSSA) Mirtazapine

Classes

- Monoamine oxidase inhibitors **(MAOIs)**
    - Tricyclic antidepressants (TCAs)
- Selective serotonin reuptake inhibitors **(SSRIs)**
- Serotonin-norepinephrine reuptake inhibitors **(SNRIs)**
    - Norepinephrine/noradrenaline reuptake inhibitors (NRIs aka NERIs/NARIs)
    - Dopamine reuptake inhibitors (DRIs)
- Opioids
- Selective serotonin reuptake enhancers **(SSREs)**
    - Novel antidepressants
- Tetracyclic antidepressants

Prominent members

Well-known antidepressants are:

- Fluoxetine - of the SSRI class (Prozac, Sarafem, Fluctin, Fontex, Prodep, Fludep, Lovan)
- Venlafaxine - of the SSRI class (Effexor, Efexor)
- Citalopram - of the SSRI class (Celexa, Cipramil, Talohexane)
- Paroxetine - of the SSRI class (Paxil, Seroxat, Aropax)
- Escitalopram - of the SSRI class (Lexapro, Cipralex)
- Fluvoxamine - of the SSRI class (Luvox, Faverin)
- Duloxetine - of the SSRI class (Cymbalta)

- Bupropion - of the DRI and NRI classes (Wellbutrin, Zyban)
- Amitriptyline - of the TCA class (Elavil)
- Dothiepin (Dosulepin) - of the TCA class (Prothiaden, Dothapax)

Mechanism of action

The therapeutic effects of antidepressants are believed to be related to an effect on neurotransmitters, particularly by inhibiting the monoamine transporter proteins of serotonin and norepinephrine. Selective serotonin reuptake inhibitors (SSRIs) specifically prevent the reuptake of serotonin (thereby increasing the level of serotonin in synapses of the brain), whereas earlier monoamine oxidase inhibitors (MAOIs) blocked the destruction of neurotransmitters by enzymes which normally break them down. Tricyclic antidepressants (TCAs) prevent the reuptake of various neurotransmitters, including serotonin, norepinephrine, and dopamine. Although these drugs are clearly effective in treating depression, the current theory still leaves unanswered questions. For example, concentrations in the blood build to therapeutic levels in only a few days and begin affecting neurotransmitter activity immediately. Changes in mood, however, often take four weeks or more to appear. One explanation holds that the "down-regulation" of neurotransmitter receptors—an apparent consequence of excess signaling and a process that takes several weeks—is actually the mechanism responsible for the alleviation of depressive symptoms. Another theory, based on recent research published by the National Institutes of Health in the United States, suggests that antidepressants may derive their effects by promoting neurogenesis in the hippocampus.. Recent research suggests that antidepressants act on transcription factors termed "clock genes" , which also are involved in actions of drugs of abuse and possibly in obesity

Treatment strategies

On efficacy measures, a successful antidepressant trial involves at least 50% of the test subjects on the drug responding to the medication. "Response" signifies at least a 50% reduction in depression symptoms, as opposed to "remission," which indicates a virtual elimination of depression symptoms. A number of different treatment strategies, however, may produce better results.

Switching

The American Psychiatric Association 2000 Practice Guideline for the Treatment of Patients with Major Depressive Disorder advises that where no response is achieved following six to eight weeks of treatment with an antidepressant to switch to an antidepressant in the same class, then to a different class of antidepressant.

A series of open-label studies by Michael Thase MD of the University of Pittsburgh found that more than half the patients who failed on their initial antidepressant achieved a response on their second antidepressant from the same class. (Thase ME et al. "Fluoxetine

treatment of patients with major depressive disorder who failed initial treatment with sertraline." J Clin Psychiatry. 1997 Jan;58(1):16-21.)

A 2002 double-blind study by the same author found a positive benefit among treatment-resistant patients switching either from an SSRI to a tricyclic or from a tricyclic to an SSRI. (Thase ME et al. "Double-blind switch study of imipramine or sertraline treatment of antidepressant-resistant chronic depression." Arch Gen Psychiatry. 2002 Mar;59(3):233-9.)

Augmentation and combination

For a partial response, the American Psychiatric Association advises augmenting an antidepressant with a different pharmaceutical agent. These agents may include lithium, thyroid supplementation, atypical antipsychotics, and dopamine agonists, among others. Symbyax, a combination olanzapine-fluoxetine (Zyprexa-Prozac) pill, is approved in the US for treating bipolar depression, and is being investigated for other depression indications. In general, however, there are no major augmentation studies to guide psychiatrists.

Combination strategy involves using two or more antidepressants from different classes to target more than one neurotransmitter in order to hopefully achieve a more beneficial result. Again, this is a little-studied area of antidepressant treatment.

Combining with psychotherapy

A 2000 study found that those on nefazadone (Serzone) plus a form of short-term psychotherapy called Cognitive Behavioral Analysis System of Psychotherapy (CBASP) fared significantly better (85% response, 42% remission) than those on Serzone alone (55% response, 22% remission) or CBASP alone (52% response, 24% remission). (Keller MB et al. "A comparison of nefazadone, the cognitive behavioral-analysis system of psychotherapy, and their combination for the treatment of chronic depression." N Engl J Med. 2000 May 18;342(20):1462-70.

Preventing relapse

A 2003 meta-analysis of 31 placebo-controlled antidepressant trials found that continuing with antidepressants reduced the risk of relapse by 70%. (Geddes JR et al. "Relapse prevention with antidepressant drug treatment in depressive disorders: a systematic review." Lancet. 2003 Feb 22;361(9358):653-61.)

The American Psychiatric Association advises four to five months of continuation treatment on an antidepressant following the resolution of symptoms. For patients with a history of depressive episodes, the British Association for Psychopharmacology's 2000 Evidence Based Guidelines for Treating Depressive Disorders with Antidepressants advises remaining on an antidepressant for at least six months and as long as five years or indefinitely.

Tolerance and dependence

Antidepressants are not thought to produce tolerance, although sudden withdrawal may produce adverse effects. Antidepressants create little if any immediate change in mood and require between several days and several weeks to take effect.

Antidepressants do not seem to have all of the same addictive qualities as other substances such as nicotine, caffeine, cocaine, or other stimulants. (There is, however, controversy on the definition of addiction.) Some argue that antidepressants do not meet the general requirements for the commonly-established view. While some antidepressants may cause dependence and withdrawal they do not seem to cause uncontrollable urges to increase the dose due to euphoria or pleasure. For example, if an SSRI medication is suddenly discontinued, it may produce both somatic and psychological withdrawal symptoms, a phenomenon known as "SSRI discontinuation syndrome" (Tamam & Ozpoyraz, 2002). When the decision is made to stop taking antidepressants it is common practice to "wean" off of them by slowly decreasing the dose over a period of several weeks.

It is generally not a good idea to take antidepressants without a prescription. The selection of an antidepressant and dosage suitable for a certain case and a certain person is a lengthy and complicated process, requiring the knowledge of a professional. Certain antidepressants can initially make depression worse, can induce anxiety, or can make a patient aggressive, dysphoric or acutely suicidal. In certain cases, an antidepressant can induce a switch from depression to mania or hypomania, can accelerate and shorten a manic cycle (i.e. promote a rapid-cycling pattern), or can induce the development of psychosis (or just the re-activation of latent psychosis) in a patient with depression who wasn't psychotic before the antidepressant.

Side effects

Antidepressants can often cause side effects, and an inability to tolerate these is the most common cause of discontinuing an otherwise working medication.

General

Although recent drugs may have fewer side effects, patients sometimes report severe side effects associated with their discontinuation, particularly with Paroxetine and venlafaxine. Additionally, a certain percentage of patients do not respond to antidepressant drugs. Another advantage of some newer antidepressants is they can show effects within as few as five days, whereas most take four to six weeks to show a change in mood. However, some studies show that these medications might be even more likely to result in moderate to severe sexual dysfunction. However, there are medications in trials that appear to show an improved profile in regard to sexual dysfunction and other key side effects.

MAO inhibitors can produce a potentially lethal hypertensive reaction if taken with foods that contain high levels of tyramine, such as mature cheese, cured meats or yeast extracts. Likewise, lethal reactions to both prescription and over the counter medications have occurred. Any patient currently undergoing therapy with an MAO inhibiting medication should be monitored closely by the prescribing physician and always consulted before taking an over the counter or prescribed medication. Such patients should also inform emergency

room personnel and information should be kept with one's identification indicating the fact that the holder is on MAO inhibiting medications. Some doctors even suggest the use of a medical alert ID bracelet. Although the reactions in question are dramatic when they happen, the total number of deaths due to interactions and dietary concerns are comparable to over-the-counter medications.

Antidepressants should be used with great care, usually in conjunction with mood stabilisers, in the treatment of bipolar disorder, as they can exacerbate symptoms of mania. They have also been known to trigger mania or hypomania in some patients with bipolar disorder and in a small percentage of patients with depression. SSRIs are the antidepressants most frequently associated with this side effect.

Use of antidepressants should be monitored by a psychiatrist, but in countries such as New Zealand, the United Kingdom, and the United States, primary care physicians are able to prescribe antidepressants without consulting a psychiatrist. In particular, it has been noted that the most dangerous period for suicide in a patient with depression is immediately after treatment has commenced, as antidepressants may reduce the symptoms of depression such as psychomotor retardation or lack of motivation before mood starts to improve. Although this appears to be a paradox, studies indicate the suicidal ideation is a relatively common component of the initial phases of antidepressant therapy, and it may be even more prevalent in younger patients such as pre-adolescents and teenagers. It is strongly recommended that other family members and loved ones monitor the young patient's behavior, especially in the first eight weeks of therapy, for any signs of suicidal ideation or behaviors. Until the black box warnings on these drugs were issued by FDA as well as by agencies in other nations, side effects and alerting families to risk were largely ignored and downplayed by manufacturers and practitioners. This may have resulted in some deaths by suicide although direct proof for such a link is largely anecdotal. The higher incidence of suicide ideation reported in a number of studies has drawn attention and caution in how these drugs are used.

Sexual

Sexual dysfunction is a very common side effect, especially with SSRIs. Bupropion, a dual reuptake inhibitor (NE and DA), in many cases results in a moderately increased libido, due to increased dopamine activity. This effect is also seen with dopamine reuptake inhibitors, CNS stimulants and dopamine agonists, and is due to increases in testosterone production (due to inhibition of prolactin) and increased nitric oxide synthesis. Apomorphine, nefazodone and nitroglycerin have been shown to reverse some sexual dysfunction via increased nitric oxide activity. MAOIs are reported to have fewer negative effects on sexual function and libido, particularly moclobemide at a 1.9% rate of occurrence. Betanechol has been reported to reverse MAOI-induced sexual dysfunction via its cholinergic agonist properties **(Gross 1982)**.

In order for the physician to select the appropriate response, the patient should provide the physician with information to distinguish between reduced libido (little or no desire for sex), reduced sexual function (impotence, vaginal dryness) and anorgasmia, as these have separate causes and prompt different treatment.

REM Sleep

It is well recognized that virtually all major antidepressant drugs suppress REM sleep and it has, in fact, been proposed that the clinical efficacy of these drugs largely derives from their suppressant effects on REM sleep. The three major classes of antidepressant drugs, monoamine oxidase inhibitors (MAOIs), tricyclic antidepressants (TCAs) and selective serotonin reuptake inhibitors (SSRIs), profoundly suppress REM sleep The MAOIs virtually completely abolish REM sleep, while the TCAs and SSRIs have been shown to produce immediate (40-85%) and sustained (30-50%) reductions in REM sleep. Ironically, a common side effect of most antidepressants is an increase in vivid dreams, and nightmares are a common result of rapid withdrawal from MAOIs.

Opioids

Opium has long been known as an antidepressant. Various Opiates were commonly used as antidepressants until the mid-1950s, when they fell out of favor with medical orthodoxy due to their addictive nature, the tolerance buildup issues and their side-effect profile.

Today the use of opioids in treating depression is a large taboo in the medical field due to associations with drug abuse; hence, research has proceeded at a very slow rate.

A small clinical trial conducted at Harvard Medical School in 1995, demonstrated that a majority of treatment-refractory, unipolar, non-psychotic, major depression patients could be successfully treated with an opioid medication called Buprenorphine, which is a partial mu agonist and potent kappa antagonist. The exact mechanism of its action in depression is not known, as kappa antagonists are antidepressants in their own right. After the release of this paper, use of buprenorphine against depression in the clinical setting has increased. The lack of large-scale clinical trials has been a deterrent to widespread use.

While opioids have been proven to substantially relieve symptoms of depression for a large class of patients, re-acceptance of this fact has been severely hampered by governmental narcotic prohibition efforts, and the (until buprenorphine) lack of alternatives with low risk of tolerance and addiction.

Buprenorphine is generally preferred as the first-line opiate in depression treatment, as managing the tolerance buildup of other opiates can be complicated.

Gamma-Hydroxybutyric acid

Gamma-Hydoxybutyric acid (GHB) has been used by some as an antidepressant. Claude Rifat, a French biologist, conducted some early research into GHB's antidepressant potential. Rifat noted that GHB did not cause the emotional blunting effects caused by conventional antidepressants, but instead intensified pleasurable and rewarding feelings in the user while powerfully suppressing depression. Unfortunately, GHB has now been outlawed, except for use as a prescription treatment for narcolepsy.

Controversy

Several studies have stimulated doubt about the effectiveness of antidepressants. The studies cite that the difference between antidepressants and placebo is negligible (Kirsch I, Moore TJ, Scoboria A, Nicholls SS (2002a), The emperor's new drugs: an analysis of antidepressant medication data submitted to the U.S. Food and Drug Administration. Prevention & Treatment 5:Article 23).

The paper in question has been severely criticized by independent researchers, however. One reason for this is that it deals almost exclusively with the SSRI class of medication. In leveling criticism against the efficacy of SSRIs, critics state, it is not the best paper, merely the most widely known one. Also, other classes of antidepressants have demonstrated superior efficacy, and it has been argued that this paper is "throwing the baby out with the bathwater", while its thrust should in fact be levelled at the serotonin hypothesis of depression.

Through a Freedom of Information Act request, two psychologists obtained 47 studies used by the FDA for approval of the six antidepressants prescribed most widely between 1987-99. Overall, antidepressant pills worked 18% better than placebos, a statistically significant difference, "but not meaningful for people in clinical settings," says University of Connecticut psychologist Irving Kirsch. He and co-author Thomas Moore released their findings in "Prevention and Treatment," an e-journal of the American Psychological Association.

More than half of the 47 studies found that patients on antidepressants improved no more than those on placebos, Kirsch says. "They should have told the American public about this. The drugs have been touted as much more effective than they are." He says studies finding no benefit have been mentioned only on labeling for Celexa, the most recently approved drug. The others included in his evaluation: Prozac, Paxil, Zoloft, Effexor and Serzone.

Additional papers have been published regarding the benefits of atypical vs. typical antidepressants. These are timely papers given the need for evidence based medicine, as well as the cost of health care. Discussion of a key paper reviewing this topic titled "Quantitative analysis of sponsorship bias in economic studies of antidepressants" can be found at an on-line journal club.

Peter Glenmullen, a Harvard psychiatrist, has written a book on the subject for the layperson; see link below.

Alternative medicines

Alternative treatments for depression such as the herbal remedy St John's wort and the amino acid derivative SAM-e have gained popularity in recent years. Clinical trials have shown the effect of acupuncture to be comparable with amitriptyline; in addition, acupuncture has been found to be more effective in depressive patients with decreased excretion of 3-methyl-4-hydroxy-phenylglycol (the principal metabolite of the central neurotransmitter norepinephrine), while amitriptyline is more effective for those with inhibition in the dexamethasone suppression test (World Health Organisation, Acupuncture: Review and Analysis of Reports on Controlled Clinical Trials, 2002). Acupuncture has also been proven to prompt the body to produce greater levels of endorphins.Clinical trials have shown SAM-e to be as effective as standard antidepressant medication, with many fewer side

effects (Delle Chiaie et al., 2002; Mischoulon and Fava, 2002). Most studies conclude that St. John's wort is usually as effective against depressions as other modern medication, again with fewer side effects, and it is widely prescribed for depression in Europe. However, a recent study showed St. John's wort to be no more effective than a placebo in cases of severe depression (Hypericum Depression Trial Study Group, 2002). Tryptophan dietary supplements, although banned in many countries due to impurities that caused a blood disease, have also been used as natural antidepressants. Dietary supplements of 5-HTP, a chemical the body forms from tryptophan and uses to make serotonin, have shown some promising research results but need further study.

Developments

NMDA antagonists such as ketamine and dextromethorphan have recently gained some interest in this field as their apparent ability to reverse endogenous opioid tolerance can give fast-acting dramatic effects. However, their acute psychoactive effects have been a problem.[1]

Memantine, a moderate affinity NMDA antagonist, has been used to avoid tolerance buildup, and has seen use in opioid tolerance reversal. Proglumide is used to induce acute reversal of tolerance prior to this maintenance strategy; it does not work by itself in the long term, due to tolerance to its effects.

References

- Roberto Delle Chiaie, Paolo Pancheri and Pierluigi Scapicchio. (2002). Efficacy and tolerability of oral and intramuscular S-adenosyl- L-methionine 1,4-butanedisulfonate (SAMe) in the treatment of major depression: comparison with imipramine in 2 multicenter studies. Am J Clin Nutr, 76 (5): 1172S-1176S
- Mischoulon D, Fava M. (2002). Role of S-adenosyl-L-methionine in the treatment of depression: a review of the evidence. Am J Clin Nutr, 76 (5): 1158S-61S.
- Hypericum Depression Trial Study Group (2002). Effect of Hypericum perforatum (St John's Wort) in Major Depressive Disorder: A Randomized Controlled Clinical Trial. JAMA, 287 (14):1807-1814.
- Acupuncture: Review and Analysis of Reports on Controlled Clinical Trials, World Health Organisation (2002)
- David Healy, The Antidepressant Era, Paperback Edition, Harvard University Press 1999

1. ^ "Drug 'treats depression in hours'", BBC, 2006-08-07. Retrieved on 2006-09-17.

Bicyclic antidepressants

Bicyclic antidepressants are a class of antidepressant drugs. They are named after the drugs' molecular structure, which contains two rings of atoms (compare tetracyclic and tricyclic antidepressants). The term 'bicyclic antidepressant' is of lesser usage than the terms tricyclic or tetracyclic subtypes since for most bicyclic structured antidepressant drugs their pharmacological identity is largely defined not by their structure but their mode of action. An example of this is Fluoxetine, though structurally bicyclic, is categorized among selective serotonin reuptake inhibitors.

See also

- antidepressant
- tetracyclic antidepressant

Monoamine oxidase inhibitors

Monoamine oxidase inhibitors (*MAOIs*) are a class of antidepressant drugs prescribed for the treatment of depression. They are particularly effective in treating atypical depression, and have also shown efficacy in helping smokers to quit. Due to potentially lethal dietary and drug interactions they had been reserved as a last line of defense, used only when other classes of antidepressant drugs (for example tricyclic antidepressants and selective serotonin reuptake inhibitors) had been tried unsuccessfully. Recently however, a patch form of the drug (known as Emsam) was invented. (Emsam was approved for use by the FDA on February 28, 2006.) When applied transdermally the drug does not enter the gastro-intestinal system as it does when taken orally, thereby decreasing the dangers of dietary interactions associated with MAOI pills.

Uses

Therapeutic use

In the past they were prescribed for those resistant to tricyclic antidepressant therapy, but newer MAOIs are now sometimes used as first-line therapy. They are also used for treating agoraphobia and social anxiety. Currently, the availability of Selegiline and moclobemide provides a safer alternative, although not always as effective as the old types.

Traditional and entheogenic use

Monoamine oxidase inhibitors can be used to potentiate the effect of a number of hallucinogenic drugs, notably phenethylamines, tryptamines and several others.

Ayahuasca, an entheogenic brew traditionally used in strict ritual context by South American native tribes, is a mixture of Banisteriopsis caapi, a vine containing various

harmala alkaloids, and another plant containing N,N-DMT or 5-MeO-DMT alkaloids, usually Psychotria viridis or Diplopterys cabrerana. Modern, western analogues to ayahuasca often substitute Syrian Rue for B. caapi and Mimosa hostilis as a DMT source. As DMT is inactive orally on its own, it must be combined with an MAOI when taken orally in order to cause psychedelic effects.

Mode of action

MAOIs act by inhibiting the activity of monoamine oxidase preventing the breakdown of monoamine neurotransmitters and so increasing the available stores. There are two isoforms of monoamine oxidase, MAO-A and MAO-B. MAO-A preferentially deaminates serotonin, melatonin, adrenaline and noradrenaline. MAO-B preferentially deaminates phenylethylamine and trace amines. Dopamine is equally deaminated by both types. Many formulations use forms of fluoride attached to assist getting past the blood-brain barrier and is suspected as a factor in pineal gland effects.

Reversibility

The early MAOIs inhibited monoamine oxidase irreversibly. When they react with monoamine oxidase, they permanently deactivate it, and the enzyme cannot function until it has been replaced by the body, which can take about two weeks. A few newer MAOIs, notably moclobemide, are reversible, meaning that they can inhibit the enzyme for a time, but eventually detach, allowing the enzyme to function once more.

Selectivity

In addition to reversibility, MAOIs differ by their selectivity of the MAO receptor. Older MAOIs inhibit both MAO-A and MAO-B equally, but newer MAOIs have been developed that target one over the other. For example, a 300 mg dose of moclobemide (Manerix, Aurorix) causes 80% inhibition of MAO-A and 20-30% inhibition of MAO-B.

Dangers

When ingested orally, MAOIs inhibit the catabolism of dietary amines. Sufficient intestinal MAO-A inhibition can lead to hypertensive crisis, when foods containing tyramine are consumed (so-called "cheese reaction"), or hyperserotonemia if foods containing tryptophan are consumed. The amount required to cause a reaction exhibits great individual variation and depends on the degree of inhibition, which in turn depends on dosage and selectivity.

The exact mechanism by which tyramine causes a hypertensive reaction is not well understood, but it is assumed that tyramine displaces norepinephrine from the storage vesicles. This may trigger a cascade in which excessive amounts of norepinephrine can lead to a hypertensive crisis. Another theory suggests proliferation and accumulation of catecholamines causes hypertensive crises. Because tyramine is the building block of

catecholamines (including dopamine, norepinephrine, and epinephrine), intake promotes production of these neurotransmitters. Excessive accumulation can result when MAO is inhibited, producing SNS effects of increased heart rate and vasoconstriction that lead to hypertension. Hypertensive crises can sometimes result in stroke or cardiac arrhythmia if not treated. This risk is generally not present with RIMAs. Both kinds of intestinal MAO-inhbition can cause hyperpyrexia, nausea and psychosis if foods high in levodopa are consumed.

Examples of foods and drinks with potentially high levels of tyramine include fermented substances, such as Chianti and other aged wines, and aged cheeses. Liver is also a well-known source. (See a list of foods containing tyramine). Examples of levodopa-containing foods include broad beans. These diet restrictions are not necessary for those taking selective MAO-B inhibitors.

It deserves separate mention that some meat extracts and yeast extracts (Bovril, Marmite, Vegemite) contain extremely high levels of tyramine, and should not be used with these medications.

When MAOI's were first introduced, these risks were not known, and over the following four decades, less than 100 people have died from hypertensive crisis. Presumably due to the sudden onset and violent appearance of the reaction, MAOI's gained a reputation for being so dangerous that, for a while, they were taken off the market in America entirely. It is now known that, used as directed under the care of a qualified psychiatrist, this class of drugs remains the safest alternative for intermediate- to long-term use.

The most significant risk associated with the use of MAOIs, is the potential for interactions with over-the-counter and prescription medicines, illicit drugs and certain supplements (e.g. St. John's Wort). It is vital that a doctor supervise such combinations to avoid adverse reactions. For this reason, many users carry an MAOI-card, which lets emergency medical personnel know what drugs to avoid. (E.g. adrenaline dosage should be reduced by 75%, and duration is extended)

MAOIs should not be combined with other psychoactive substances (antidepressants, illicit drugs, painkillers, stimulants, etc.) except under expert care. Certain combinations can cause lethal reactions, common examples including SSRIs, tricyclics, meperidine and tramadol. Agents with actions on epinephrine, norepinephrine or dopamine must be administered at much lower doses due to potentiation and prolonged effect. Purely opiate-acting analgesics, such as morphine and buprenorphine may be used safely with MAOIs, but may require a dosage adjustment.

List of MAOIs

Monoamine oxidase inhibitors include:

- Isocarboxazid (Marplan)

Moclobemide (Aurorix, Manerix, Moclodura®)
Phenelzine (Nardil)
Tranylcypromine (Parnate)
Selegiline (Selegiline, Eldepryl), and Emsam
Nialamide
Iproniazid (Marsilid, Iprozid, Ipronid, Rivivol, Propilniazida)

Iproclozide
Toloxatone
Many tryptamines have MAOI properties. Harmine (present in Harmal, Banisteriopsis caapi, and tobacco) is a powerful MAOI, which is often used as one of the ingredients of ayahuasca. Certain others as AMT, 5-MeO-DMT or 5-MeO-AMT provide only minor MAO inhibition.

Reversible inhibitors of MAO-A

*RIMA*s (reversible inhibitors of monoamine oxidase type-A) are a family of psychiatric drugs that inhibit monoamine oxidase, temporarily and reversibly. They are mostly used for alleviating depression and dysthymia.

Because their action is short-lived and selective, they have a better safety profile than the older MAOI drugs (monoamine oxidase inhibitors). A special diet does not need to be so strictly adhered to, although eating excessively large amounts of tyramine-containing foods is not advisable.

Combining a RIMA or MAOI with an SSRI is dangerous since it can lead to serotonin syndrome and possible fatality.

Moclobemide and Brofaromine are RIMAs.

Harmala alkaloid

The *Harmala alkaloid* "Harmine", also known as *Telepathine* and *Banisterine*, is a naturally occurring beta-carboline alkaloid that is structurally related to harmaline. Harmine and harmaline are reversible monoamine oxidase inhibitors. They can stimulate CNS by inhibiting the metabolism of serotonin and other monoamines.

Some harmala alkaloids, particularly harmine and harmaline, are found in the seeds of the Middle Eastern plant Harmal (Peganum harmala, from which the name derives), commonly known as Syrian Rue. They occur in the seeds in concentrations of roughly 3%, though tests have documented anywhere from 2-7%, as natural sources tend to vary widely in chemical makeup. Harmala alkaloids are also found in the vine Banisteriopsis caapi in concentrations that range between 0.31-8.43% for harmine, 0.03-0.83% for harmaline and 0.05-2.94% for tetrahydroharmine [THH].[1] Banisteriopsis caapi is the key plant ingredient in the sacramental beverage Ayahuasca. Leaves from "Psychotria viridis", a source of DMT, are often added to Ayahuasca to achieve visionary states of consciousness. Many other psychoactive plants are known to be added to , as the harmala alkaloids are not significantly psychoactive on its own.

Harmala alkaloids are also found in many other plants, such as tobacco and passion flower.

Telepathine

Telepathine was originally thought to be the active chemical constituent of Banisteriopsis caapi, a key plant ingredient in the preparation of Ayahuasca; a sacremental beverage from the Amazon. This isolated chemical was so named because of the reported effects of Ayahuasca among the indigenous users, including: collective contact with and/or visions of jaguars, snakes, and jeweled birds, and ancestral spirits; the ability to see future events; and as the name suggests, telepathic communication among tribal members. It was assumed to be a newly discovered chemical at the time, however, it was soon realized that Telepathine was already more widely known as Harmine from its previous discovery in Syrian Rue (Peganum harmala).

Uses

As mentioned above, some harmala alkaloids can be used as an MAOI (*M*ono*A*mine *O*xidase *I*nhibitor) to facilitate the oral ingestion of DMT and other tryptamines; it is not hallucinogenic on its own. In high doses, it acts a purgative. Harmala alkaloids from Banisteriopsis caapi have been used to treat Parkinson's disease. Additionally, Harmaline is used as a model for Essential Tremor when injected to animals. Rats being treated with Harmaline exhibit severe tremors after 5-7 minutes. In-Vitro research showed that Harmaline increased subthreshold oscillations in neuronal membrane potential in a brainstem slice preparation containing the Inferior Olive.

References

1. ^ Callaway JC, Brito GS & Neves ES (2005). Phytochemical analyses of Banisteriopsis caapi and Psychotria viridis. Journal of Psychoactive Drugs 37(2): 145-150.

Chemical Forms

- *Harmine*: $C_{13}H_{12}N_2O$

7-Methoxy-1-methyl-9H-pyrido[3,4-b]indole

- *Harmaline*: $C_{13}H_{14}N_2O$

4,9-Dihydro-7-methoxy-1-methyl-3H-pyrido[3,4-b]indole

- Tetrahydroharmine*: $C_{13}H_{16}N_2O_4P$*

7-Methoxy-1,2,3,4-Tetrahydro-Harmine

- *Harmine acid*: methylester:

Methyl-7-methoxy-b-carboline-1-carboxylate

- Harmilinic acid*:*

7-methoxy-3,4-dihydro-b-carboline1-carboxylic acid

- Harmanamide*:*

1-carbamoyl-7-methoxy-b-carboline

- Acethylnorharnine*:*

1-acethyl-7-methoxy-b-carboline

See also

- monoamine oxidase inhibitors

List of foods containing tyramine

This is a *list of foods containing tyramine*. Tyramine is an amine which causes elevated blood pressure and tachycardia by displacing norepinephrine from storage vesicles. Tyramine is generally produced by decarboxylation of the amino acid tyrosine during fermentation of food products. All protein rich food which has been matured will contain more tyramine depending on the temperature and for how long it has been stored. Properly refrigerated will not be effected.

The amount required to cause a 30mmHg increase in diastolic blood pressure is referred to as TYR30, and generally averages around 500mg in an unmedicated, healthy individual. A class of antidepressants called MAOIs (monoamine oxidase inhibitors) can increase the sensitivity to tyramine if taken orally. If sufficient quantities of tyramine are ingested, hypertensive crises may occur, potentially causing stroke or cardiac arrythmia. There is significant evidence that tyramine may trigger migraines in sensitive individuals.

This list is for informational purposes only; it is neither all-inclusive nor does it go into any particular depth. If you plan to avoid tyramine in your diet, you are urged to seek professional guidance. Note that the exact increase in sensitivity will depend on the MAOI used, and its dose.

Alcoholic Beverages

All tap beer and ale should be avoided, as lack of hygiene and proper maintenance may allow tyramine-forming bacteria to grow. Domestic bottled beers are generally safe in small quantities. Red wine and white wine are acceptable as long as no more than 120ml is ingested. Chianti and vermouth, however, should be avoided.

Cheeses

Most aged cheeses should be avoided. While there are some, such as cream cheese and cottage cheese, that have little to no notable amounts of tyramine, most aged cheeses have high concentrations of tyramine. It is therefore wise for people that are sensitive to tyramine to avoid all aged cheeses, if at all possible.

Regular cheese of the kind typically used on bread and pizza can safely be consumed in normal amounts.

Fruit

Avocados contain tyramine, especially overripe fruit. Avocados may be eaten in moderate quantities, provided that the fruit is not overripe. Banana peels contain significant levels of tyramine.

All other fruits should be eaten in moderation, since overripe and dried fruit will contain more tyramine. Common fruits that may contain relevant levels of tyramine include: eggplant, figs, grapes, oranges, pineapples, plums, prunes and raisins.

Processed Foods

Many processed foods should be avoided, due to high tyramine levels. A few processed foods that contain high amounts of tyramine include, but are not limited to: vegemite, sauerkraut, and shrimp paste.

Meat and Fish

Fresh liver has no significant levels of tyramine, but old liver contains high amounts. Like liver, fresh meat and fish are safe, and old meat is risky. Caution is recommended in restaurants or any other uncertain source of meat. Traditionally meat from game birds and wild animals, is hung in a cool place to improve the flavour and tenderness, this significantly increases the tyramine content. Processed meats, cured or pickled meats, and meat by products and broths often contain large amounts of tyramine.

Soy

All soy products contain high levels of tyramine. Aside from soybeans themselves, commonly consumed soy products include: soy sauce, tofu, miso, and teriyaki sauce. The quantities of these products should be limited.

Nuts and Chocolate

Chocolate does not contain appreciable amounts of tyramine, but does contain other active ingredients that are potentiated by MAOIs. Accordingly, chocolate should be limited to moderate quantities to avoid risk of nausea, headaches, temperature changes and psychosis.

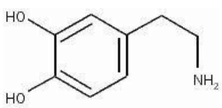
There is some evidence that large quantities of nuts, peanuts, coconuts, and brazil nuts may trigger hypertensive reactions and headaches.

Monoamine reuptake inhibitors

Dopamine reuptake inhibitors | Selective serotonin reuptake inhibitor **|** Serotonin-norepinephrine reuptake inhibitor

Dopamine

Dopamine



General

Systematic name	**4-(2-aminoethyl)benzene-1,2-diol**
Other names	**2-(3,4-dihydroxyphenyl)ethylamine; 3,4-dihydroxyphenethylamine; 3-hydroxytyramine; DA; Intropin Revivan; Oxytyramine**
Molecular formula	**$C_8H_{11}NO_2$**
SMILES	**C1=CC(=C(C=C1CCN)O)O**
Molar mass	**153.178 g/mol**
Appearance	**white powder with distinctive smell**
CAS number	**[51-61-6]**

Properties

Solubility in water	**60.0 g/100 ml (? °C), solid**
Melting point	**128 °C (401 K)**
Hazards	
R/S statement	**R: 36/37/38** **S: 26-36**
RTECS number	**UX1088000**
Except where noted otherwise, data are given for materials in their standard state (at 25 °C, 100 kPa)	

Dopamine is a chemical naturally produced in the body. In the brain, dopamine functions as a neurotransmitter, activating dopamine receptors. Dopamine is also a neurohormone released by the hypothalamus. Its main function as a hormone is to inhibit the release of prolactin from the anterior lobe of the pituitary.

Dopamine can be supplied as a medication that acts on the sympathetic nervous system, producing effects such as increased heart rate and blood pressure. However, since dopamine cannot cross the blood-brain barrier, dopamine given as a drug does not directly affect the central nervous system. To increase the amount of dopamine in the brains of patients with diseases such as Parkinson's disease and Dopa-Responsive Dystonia, a synthetic precursor to dopamine such as L-DOPA can be given, since this will cross the blood-brain barrier.

Contents

Biochemistry

Dopamine has the chemical formula ($C_6H_3(OH)_2$-CH_2-CH_2-NH_2). Its chemical name is 4-(2-aminoethyl)benzene-1,2-diol and it is abbreviated "DA."

As a member of the catecholamine family, dopamine is a precursor to epinephrine (adrenaline) and norepinephrine (noradrenaline) in the biosynthetic pathways for these neurotransmitters. Arvid Carlsson won a share of the 2000 Nobel Prize in Physiology or Medicine for showing that dopamine is not just a precursor to these, but a neurotransmitter as well.

Dopamine is synthesized in the body (mainly by nervous tissue and adrenal glands) first by the hydration of the amino acid tyrosine to DOPA by tyrosine hydroxylase and then by the decarboxylation of DOPA by aromatic-L-amino-acid decarboxylase. In neurons, dopamine is packaged after synthesis into vesicles, which are then released in response to the presynaptic action potential. The inactivation mechanism of neurotransmission are 1) uptake via a specific transporter; 2) enzymatic breakdown; and 3) diffusion. Uptake back to the presynaptic neuron via the dopamine transporter is the major role in the inactivation of dopamine neurotransmission. The recycled dopamine will face either breakdown by an enzyme or be re-packaged into vesicles and reused.

Functions in the brain

Dopamine has many functions in the brain. Most importantly, dopamine is central to the reward system. Dopamine neurons may have the role to emit a teaching signal for prioritizing and learning of reward-directed behaviour and to code reward information relative to established predictions.

Movement

Dopamine affects the basal ganglia motor loop which in turn affects the way the brain controls our movements. Shortage of dopamine, particularly the death of dopamine neurons

in the nigrostriatal pathway, causes Parkinson's disease, in which a person loses the ability to execute smooth, controlled movements.

Cognition and frontal cortex

In the frontal lobes, dopamine controls the flow of information from other areas of the brain. Dopamine disorders in this region of the brain can cause a decline in neurocognitive functions, especially memory, attention and problem-solving. Reduced dopamine concentrations in the prefrontal cortex are thought to contribute to attention deficit disorder and negative schizophrenia. Conversely, anti-psychotic medications rely on their inhibition of dopamine uptake and are used in the treatment of positive symptoms in schizophrenia.

Regulating prolactin secretion

Dopamine is the primary neuroendocrine regulator of the secretion of prolactin from the anterior pituitary gland. Dopamine produced by neurons in the arcuate nucleus of the hypothalamus is secreted into the hypothalamo-hypophysial blood vessels of the median eminence, which supply the pituitary gland. The lactotrope cells that produce prolactin, in the absence of dopamine, secrete prolactin continuously; dopamine inhibits this secretion.

Motivation and pleasure

Dopamine is commonly associated with the pleasure system of the brain, providing feelings of enjoyment and reinforcement to motivate a person proactively to perform certain activities. Dopamine is released (particularly in areas such as the nucleus accumbens and striatum) by naturally rewarding experiences such as food, sex, use of certain drugs and neutral stimuli that become associated with them. This theory is often discussed in terms of drugs (such as cocaine and amphetamines), which seem to be directly or indirectly related to the increase of dopamine in these areas, and in relation to neurobiological theories of chemical addiction, arguing that these dopamine pathways are pathologically altered in addicted persons. However, cocaine and amphetamine influence separate mechanisms of action.

Cocaine is a dopamine transporter blocker that competitively inhibits dopamine uptake to increase the lifetime of dopamine and augments an overabundance of dopamine (an increase of up to 150%) within the parameters of the dopamine neurotransmitters. Like cocaine, amphetamines increase the concentration of dopamine in the synaptic gap, but by a different mechanism. Amphetamines are similar in structure to dopamine, and so can enter the terminal button of the presynaptic neuron via its dopamine transporters as well as by diffusing through the neural membrane directly. When entering inside the presynaptic neuron, amphetamines force the dopamine molecules out of their storage vesicles and expel them into the synaptic gap by making the dopamine transporters work in reverse.

Dopamine's role in experiencing pleasure has been questioned by several researchers. It has been argued that dopamine is more associated with anticipatory desire and motivation (commonly referred to as "wanting") as opposed to actual consummatory pleasure (commonly referred to as "liking"). Dopamine is released when unpleasant or aversive stimuli are encountered, and so motivates towards the pleasure of avoiding or removing the unpleasant stimuli.

Recent research suggests that the firing of dopamine neurons is a motivational chemical as a result of reward-anticipation. This is based on evidence that, when a reward is perceived to be greater than expected, the firing of certain dopamine neurons increases, which correspondingly increases desire or motivation toward the reward.

Clues to dopamine's role in motivation, desire and pleasure have come from studies performed on animals. In one such study rats were depleted of dopamine by up to 99% in the nucleus accumbens and neostriatum using 6-hydroxydopamine.[1] With this large reduction in dopamine, the rats would no longer eat by their own volition. The researchers then force fed the rats food and noted whether they had the proper facial expressions indicating whether they liked or disliked it. The researchers of this study concluded that the reduction in dopamine did not reduce the rat's consummatory pleasure, only the desire to actually eat. In another study, mutant hyperdopaminergic (increased dopamine) mice show higher "wanting" but not "liking" of sweet rewards.[2]

In humans, though, drugs that reduce dopamine activity (e.g., antipsychotics) have been shown to reduce motivation as well as cause anhedonia (the inability to experience pleasure).[3] Conversely the selective D2/D3 agonists pramipexole and ropinirole have anti-anhedonic properties as measured by the Snaith-Hamilton Pleasure Scale.[4] (The Snaith-Hamilton-Pleasure-Scale (SHAPS), introduced in English in 1995, assesses self-reported anhedonia in psychiatric patients.)

Opioid and cannabinoid transmission instead of dopamine may modulate consummatory pleasure and food palatability(liking).[5] This could explain why animals "liking" of food is independent of brain dopamine concentration. Other consummatory pleasures, however, may be more associated with dopamine. One study found that both anticipatory and consummatory measures of sexual behavior (male rats) were disrupted by DA receptor antagonists.[6] Libido can be increased by drugs that affect dopamine but not by drugs that affect opioid peptides or other neurotransmitters.

Sociability is also closely tied to dopamine neurotransmission. Low D2 receptor binding is found in people with social anxiety. Traits common to negative schizophrenia (social withdrawal, apathy, anhedonia) are thought to be related to a hypodopaminergic state in certain areas of the brain. In instances of bipolar, manic subjects can become hypersocial as well as hypersexual. This is also credited to an increase in dopamine, because mania alleviates from dopamine blocking antipsychotics.

Other theories reinforce that the crucial role of dopamine may be in desire, or anticipating pleasurable activity. Related theories [7] argue that dopamine function may be involved in the salience ('noticeableness') of perceived objects and events, with potentially important stimuli such as: 1) rewarding things or 2) dangerous or threatening things seeming more noticeable or important. This hypothesis argues that dopamine assists decision-making by influencing the priority, or level of desire, of such stimuli to the person concerned.

Pharmacological blockade of brain dopamine receptors increases rather than decreases drug-taking behavior. Since blocking dopamine decreases desire, the increase in drug taking behavior may be seen as not a chemical desire but as a deeply psychological desire to just 'feel something'.

Deficits in dopamine levels are implicated as one of several possible causes for Adult attention-deficit disorder (AADD), and some types of medications used to treat Attention-deficit hyperactivity disorder (ADHD/ADD) will help to stimulate dopaminergic systems, leading to potentially heightened sensation, for those afflicted by it and receiving treatment for it.

Links to psychosis

Disruption to the dopamine system has also been strongly linked to psychosis and schizophrenia.[8] Dopamine neurons in the mesolimbic pathway are particularly associated with these conditions. This is partly due to the discovery of a class of drugs called the phenothiazines (which block D2 dopamine receptors) that can reduce psychotic symptoms, and partly due to the finding that drugs such as amphetamine and cocaine (which are known to greatly increase dopamine levels) can cause psychosis. Because of this, most modern antipsychotic medication is designed to block dopamine function to varying degrees.

Depression

Dopamine is a neurotransmitter that is involved in depression. Amphetamines and dopamine reuptake blockers have potent anti-depressant effects but these drugs quickly lose their benefit after they deplete dopamine levels in the brain. Antidepressants appear to primarily enhance serotonergic neurotransmission during preliminary drug administration but it takes several weeks for the antidepressant effect to be noticed. The late effect of antidepressants is thought to involve the indirect serotonergic modulation of dopaminergic neurotransmission. Blocking the D***2*** dopamine receptor is known to cause relapse in patients that have achieved remission from depression, and such blocking also counteracts the effectiveness of SSRI medication.

Therapeutic use

Levodopa is a dopamine precursor used to treat Parkinson's disease. It is typically co-administered with an inhibitor of peripheral decarboxylation (DDC, dopa decarboxylase), such as carbidopa or benserazide. Inhibitors of alternative metabolic route for dopamine by catechol-O-methyl transferase are also used. These include entacapone and tolcapone.

Dopamine is also used as an inotropic drug in patients with shock to increase cardiac output and blood pressure.

Major pathways

- Mesocortical pathway
Mesolimbic pathway
Nigrostriatal pathway
Tuberoinfundibular pathway

See also

- Amphetamine
- Antipsychotic
- Cocaine
- Dopamine reuptake inhibitors
- Methylphenidate
- Parkinson's disease

Footnotes

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7. ^ Schultz W (2002). "Getting formal with dopamine and reward". Neuron *36* (2): 241-263. PMID 12383780.
8. ^ Disruption of gene interaction linked to schizophrenia. St. Jude Children's Research Hospital. Retrieved on 2006-07-06.

Amphetamines

Systematic (IUPAC) name 1-phenylpropan-2-amine

Identifiers

CAS number rn=1" href="http://www.nlm.nih.gov/cgi/mesh/2006/MB_cgi?term=300-62-9&rn=1"> 300-62-9

ATC code **N06**BA01

PubChem 3007

DrugBank APRD00480

Chemical data

Formula $C_9H_{13}N$

Mol. weight 135.2084

Pharmacokinetic data

Bioavailability 4L/kg; low binding to plasma proteins (20%)

Metabolism Hepatic

Half life 10–13 hours

Excretion Renal; significant portion unaltered

Therapeutic considerations

Pregnancy cat. C (USA)

Legal status DEA Schedule II (USA), Class B (UK), Schedule III (Canada)

Routes Oral, Intravenous, Vaporized, Insufflated, Suppository

Amphetamine (*a*lpha-*m*ethyl-phenethylamine), also known as *speed* or *crank*, is a stimulant, and *club drug*, used to diminish the appetite, control weight, and treat disorders including narcolepsy and attention-deficit hyperactivity disorder. It is also used recreationally and for performance enhancement (these uses are illegal in some countries).

Illicit production and use of amphetamines occurs on a widescale basis in several European nations, typically in the form of amphetamine sulfate synthesized from phenylpropanolamine. In addition, because of the widespread use of amphetamines as a treatment for narcolepsy and ADD/ADHD, prescription amphetamines are subject to diversion and are one of the most frequently-abused drugs in high schools and colleges.

Toxicity

Patients with acute toxicity from amphetamines may have symptoms of psychosis, disorientation, temporary symptoms associated with schizophrenia, aggression, delusions, lock-jaw, diarrhea, palpitations, arrhythmia, syncope, hyperpyrexia, and hyperreflexia progressing to convulsions and coma. Patients with chronic use of amphetamines develop a rapid tolerance to the drug and may have to increase the dose to reach the desired effect and eventually develop addiction. Patients that develop addiction show symptoms of restlessness, anxiety, depression, insomnia, and suicidal behavior. A urine drug screen can be performed to determine the presence of amphetamines. Patients may need to be hospitalized. Supportive therapy is important. Cooling blankets may be used for hyperthermia. Sedation may be obtained with lorazepam or diazepam. Haloperidol may be given for agitation and delusions. Hypertension and arrhythmias should be treated.

Chemistry

Amphetamine was first synthesized in 1887 by the Romanian chemist Lazr Edeleanu at the University of Berlin, who called it "*phenylisopropylamine*". Amphetamine is a chiral compound. The racemic mixture can be divided into its optical antipodes: levo- and dextro-amphetamine. Amphetamine is the parent compound of its own structural class, comprising a broad range of psychoactive derivatives, e.g., MDMA (Ecstasy) and the N-methylated form, methamphetamine. Amphetamine is a homologue of phenethylamine.

Traditionally the medical drug came in the racemic salt-form rac-amphetamine sulfate (rac = levo- and dextro-form in equal amounts). Today, dextroamphetamine sulphate is the predominant form of the drug used; it consists entirely of the d-isomer. Attention disorders are often treated using Adderall or generic-equivalent formulations of mixed amphetamine salts that contain both d/l-amphetamine and d-amphetamine in the sulfate and saccharate forms mixed to a final ratio of 3 parts d-amphetamine to 1 part l-amphetamine.

Pharmacology

Dextroamphetamine, the eutomer of amphetamine, exhibits its mode of peripheral action via release and reuptake inhibition of the monoamine neurotransmitters acetylcholine (ACh) and histamine (H), but not glutamate. Its activity at the vesicular monoamine transporter VMAT2 is of crucial importance in the release process.[1]

Application range

Amphetamine is a synthetic drug with strong stimulant effects. In the United States, it is most commonly used for treatment of attention-deficit disorders and narcolepsy, but is also approved as a weight-loss medication in certain cases of obesity. Within the armed forces only, it is also frequently prescribed as an anti-fatigue pill for pilots and other individuals in situations requiring vigilance and alertness. Amphetamine is also used illegally to take advantage of these effects. The wanted effects stem predominantly from d-amphetamine; l-amphetamine contributes to the unwanted peripheral side effects, primarily nausea after the dose loses effect.

Medicinal use

Indicated for:

- Diet suppressant
ADD
ADHD
Narcolepsy
Treatment-resistant depression

Recreational uses:

- Stimulant

Other uses:

- Used by the US military to combat fatigue and increase wakefulness

Contraindications:

- CNS Stimulants
- MAOI **use**

Side effects:

- Dizziness
Tachycardia
Sweating
Decrease in appetite/weight loss
Euphoria followed by depression
Insomnia
Anger
Aggressiveness
Hostility

Cardiovascular:

- Bronchodilator

Ear, nose, and throat:

- Decongestant

Eye:

- Mydriasis (Pupil dilation)

Gastrointestinal:

- Diarrhoea

Musculoskeletal:

- Muscle aches/cramps

Neurological:

- Dopamine Agonist

Norepinephrine Agonist

Respiratory:

- Bronchodilator

The experimental medical use of amphetamines began in the 1920s. It was introduced in most of the world in the form of the pharmaceutical Benzedrine in the late-1920s. The drug was used by the militaries of several nations, especially the air forces, to fight fatigue and increase alertness among servicemen. After decades of reports of abuse, the FDA banned Benzedrine inhalers, and limited amphetamines to prescription use in 1959, but illegal use became common.

Along with methylphenidate (Ritalin, Concerta, etc.), amphetamine is one of the standard treatments for ADHD. Beneficial effects for ADHD can include improved impulse control, improved concentration, decreased sensory overstimulation, and decreased irritability. These effects can be dramatic, particularly in young children. The ADHD medication Adderall is composed of four different amphetamine salts, and Adderall XR is a timed release formulation of these same salt forms.

When used within the recommended doses, side-effects like loss of appetite tend to decrease over time. However, amphetamines last longer in the body than methylphenidate (Ritalin, Concerta, etc.), and tend to have stronger side-effects on appetite and sleep.

Amphetamines are also a standard treatment for narcolepsy as well as other sleeping disorders. They are generally effective over long periods of time without producing addiction or physical dependence.

Amphetamines are sometimes used to augment anti-depressant therapy in treatment-resistant depression.

Medical use for weight loss is still approved in some countries, but is regarded as obsolete and dangerous in, for example, the United States.

Effects of use

Amphetamines release stores of norepinephrine and dopamine from nerve endings by converting the respective molecular transporters into open channels. Amphetamine also releases stores of serotonin from synaptic vesicles. Like methylphenidate (Ritalin), amphetamines also prevent the monoamine transporters for dopamine and norepinephrine from recycling them (called reuptake inhibition), which leads to increased amounts of dopamine and norepinephrine in synaptic clefts.

These combined effects rapidly increase the concentrations of the respective neurotransmitters in the synaptic cleft, which promotes nerve impulse transmission in neurons that have those receptors.

Physical effects

- Short-term physiological effects include decreased appetite, increased stamina and physical energy, increased sexual drive/response, involuntary bodily movements, hyperhidrosis, hyperactivity, jitteriness, nausea, itchy, blotchy or greasy skin, Tachycardia, irregular heart rate, hypertension, and headaches. Fatigue can often follow the dose's period of effectiveness. Overdose can be treated with chlorpromazine.
- Long-term abuse or overdose effects can include tremor, restlessness, changed sleep patterns, anxiety and increase in pre-existing anxiety, poor skin condition, hyperreflexia, tachypnea, gastrointestinal narrowing, and weakened immune system. Fatigue and depression can follow the excitement stage. Erectile dysfunction, heart problems, stroke, and liver, kidney and lung damage can result from prolonged use. When snorted, amphetamine can lead to a deterioration of the lining of the nostrils.

Psychological effects

- Short-term psychological effects can include alertness, euphoria, increased concentration, rapid talking, increased confidence, increased social responsiveness, nystagmus (eye wiggles), hallucinations, and loss of REM sleep the night after use.
- Long-term psychological effects can include insomnia, mental states resembling schizophrenia, aggressiveness (not associated with schizophrenia), addiction or dependence with accompanying withdrawal symptoms, irritability, confusion, and panic. Chronic and/or extensively-continuous use can lead to amphetamine psychosis, which causes delusions and paranoia, but this is uncommon when taken as prescribed. Amphetamine is highly-psychologically addictive, and, with chronic use, tolerance develops very quickly. Withdrawal is, although not physiologically threatening, an unpleasant experience (including paranoia, depression, difficult breathing, dysphoria, gastric fluctuations and/or pain, and lethargia). This commonly leads chronic users to re-dose amphetamine frequently, explaining tolerance and increasing the possibility of addiction.

Addiction

Tolerance is developed rapidly in amphetamine use, therefore increasing the amount of the drug that is needed to satisfy the addiction. Many abusers will repeat the amphetamine cycle by taking more of the drug during the withdrawal. This leads to a very dangerous cycle and may involve the use of other drugs to get over the withdrawal process. Chronic users of amphetamines may resort to drug injection to experience the full effect of the drug in a faster and more intense way, with the added risks of bacterial and viral tranmission, vein damage and higher risk of overdose.

Legal issues

- In the United Kingdom, amphetamines are regarded as Class B drugs. The maximum penalty for unauthorised possession is three months' imprisonment and a £2,500 fine.
- In the United States, amphetamine and methamphetamine are Schedule II controlled drugs, classified as a CNS (Central Nervous System) Stimulant. A Schedule II drug is classified as one that: has a high potential for abuse, has a currently-accepted medical use and is used under severe restrictions, and has a high possibility of severe psychological and physiological dependence.

Internationally, amphetamine is a Schedule II drug under the Convention on Psychotropic Substances[2].

Popular culture

- Avant-garde rock and roll band The Velvet Underground wrote White Light/White Heat (song), about the effects of the drug.
Blues-Rock band Canned Heat wrote a song, on the album Boogie With Canned Heat called Amphetamine Annie, about a girl who takes speed regularly.
Rock and roll band Everclear (band) wrote a song called Amphetamine, about a girl named Amphetamine.
Space-rock band Hawkwind performed a song entitled "Motorhead", written by Lemmy Kilmister shortly before forming his own band of the same name. Kilmister is known for being a longtime user of speed.
Alternative Rock band The Smashing Pumpkins mention Amphetamine in a song titled "Annie Dog" from the album "Adore".
Rock and Roll band The Sisters of Mercy were (in)famous for the constant references to amphetamine throughout their career.
Industrial Rock band Marilyn Manson mention Amphetamines in a song titled "Rock is Dead".
Punk rock band Toys That Kill have a song entitled Amphetamine St. off their album The Citizen Abortion.
Alternative Metal band Seether mention Amphetamine in a song titled "I'm The One" from the album "Karma And Effect".

Books

- Seabrook, Jeremy (1996). In the Cities of the South:scenes from a developing world. London; New York: Verso. ISBN 1-85984-986-5.

Related pages

- Adderall
- Methamphetamine **(Desoxyn)**
    - Methylphenidate (Ritalin, Concerta)
- Phenethylamines
- Stimulants

References and Notes

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2. ^ List of psychotropic substances under international control (PDF). International Narcotics Control Board. Retrieved on November 19, 2005.

3,4-Methylenedioxyamphetamine

MDA

Chemical name 3,4-Methylenedioxyamphetamine or 1-(benzo[d][1,3]dioxol-5-yl)propan-2-amine

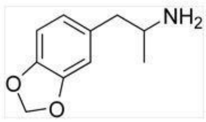
Chemical formula $C_{10}H_{13}NO_2$

Molecular mass 179.22 g/mol

Melting point 187 - 188 °C (hydrochloride)

CAS numbers 4764-17-4, 51497-09-7, 61614-60-6, 65620-66-8

SMILES NC(C)CC1=CC=C(OCO2)C2=C1



3,4-methylenedioxyamphetamine, or *MDA*, is a psychedelic hallucinogenic drug and empathogen/entactogen of the phenethylamine family. It was first synthesized by G. Mannish and W. Jacobson in 1910. There are about 20 different synthetic routes described in the literature for its preparation.

Medical use

MDA was first used in animal tests in 1939, and human trials began in 1941 in the exploration of possible therapies for Parkinson's disease. From 1949 to 1957, more than 500 human subjects were given MDA in an investigation of its potential use as an antidepressant and/or anorectic by Smith, Klein, and French. The United States Army also experimented with the drug, code named EA-1298, while working to develop a truth drug or incapacitating agent. One human subject died in January 1953 after being intravenously injected with 500mg of the drug. MDA was patented as a cough suppressant by H. D. Brown in 1958, as an ataractic by Smith, Klein, and French in 1960, and as an anorectic under the trade name “Amphedoxamine” in 1961. Several researchers, including Claudio Naranjo, have explored MDA in the field of psychotherapy.

Recreational use

MDA began to appear on the recreational drug scene around 1963 to 1964. It was then inexpensive and readily available as a research chemical from several scientific supply houses. Although now illegal, MDA continues to be bought, sold, and used for recreational purposes, often in the form of tablets purporting to contain MDMA (Ecstacy).

Effects

A recreational dose of MDA is commonly between 80 and 160mg. The “R” optical isomer is more potent than the “S” optical isomer. Although there is some debate, the duration of the drug is now generally believed to be roughly 6 to 10 hours(In the late 90s, Shulgin changed his opinion of the duration to 3-6 hours). The effects of the drug are quite similar to those of MDMA (Ecstacy), including empathogen/entactogenic effects, though typically less intense than a similar dosage of MDMA. Because of these effects, MDA was called the “hug drug” and was alleged to stand for “Mellow Drug of America” in the 1960s. Some users feel that MDA has more psychedelic or hallucinogenic qualities than MDMA.

The toxicity of MDA is not fully known. The LD50 in mice has been reported as 92mg/kg by intraperitoneal injection. Erowid lists the fatality rate at roughly 2 in 100,000 users. MDA is considered to be more potentially neurotoxic than its methylated cousin MDMA. It is a direct metabolite of MDMA.

Legality

In 1970, the Controlled Substances Act was enacted in the United States, placing MDA into Schedule I. It is similarly controlled in other nations. In Canada MDA is a Schedule III drug. Internationally, MDA is a Schedule I drug under the Convention on Psychotropic Substances[1].

See also

- Empathogen-entactogen
- Phenethylamines
- Psychedelic
    - Amphetamine

References

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    - Stafford, P. Psychedelics Encyclopedia. Ronin, 1992.

Adderall

Adderall® CII is a pharmaceutical stimulant Amphetamine used to treat attention-deficit hyperactivity disorder and narcolepsy. Severe cases of depression may also be treated with Adderall or other stimulants. It was first prescribed in the 1970s as an anorectic (under the brand name Obetrol®), but such usage is now rare.

Use

- 1/4 Dextro-amphetamine Saccharate
- 1/4 Dextro-amphetamine Sulfate
- 1/4 dl-amphetamine Aspartate (racemic Amphetamine)
- 1/4 dl-amphetamine Sulfate (racemic Amphetamine)

The four component salts are claimed to be metabolised at different rates.

The average elimination half-life for dextroamphetamine is 10 hours in adults, and for levoamphetamine, 13 hours. Its effects are otherwise similar to other central nervous system stimulants (see amphetamine for details.).

The manufacturer claims that the mixture of salts makes Adderall's effects smoother, with softer highs and lows, than those of other treatments for the same disorders.

There is little evidence, however, to support this claim for immediate-release. A recent patent application for Adderall (USP #6,384,020) was a pharmaceutical composition patent listing a rapid immediate release oral dosage form. No claim of increased or smooth drug delivery was made. A recent double-blind, placebo-controlled crossover study, conducted among children, indicated that patients behaved similarly to other immediate release amphetamines. The authors found that sustained-release dexamphetamine (the main isomeric-amphetamine component of Adderall) had a longer duration of action, and cost less than Adderall, though dexamphetamine was less effective in the first few hours

Adderall is now sold in either an immediate-release tablet or an extended-release capsule, marketed as Adderall XR (for "eXtended Release"). Doses for both immediate-release and extended-release form come in 5, 10, 15, 20, 25, 30, and 35 mg increments. Adderall XR utilizes the Microtrol® delivery system to achieve the extended-release mechanism. This delivery system incorporates two beads: the first type of bead dissolves immediately and the second type releases four hours later. Maximum plasma concentration is achieved in seven hours, compared to regular Adderall IR (immediate-release) which reaches maximum plasma concentration within three hours. As a result of its high bioavailability, Adderall XR's effectiveness is not altered by food absorption in the gastrointestinal tract. However, tmax (mean plasma concentration) is prolonged by 2.5 hours (using a standard high-fat meal as the control). Acidic beverages should not be ingested with Adderall XR as they alter the pH balance of the stomach

Effects

While the exact mechanism is unknown, it is believed that Adderall works by blocking the reuptake of dopamine and norepinephrine into the presynaptic neuron and increasing their release from the presynaptic neuron into the extraneuronal space. In other words, Adderall reverses the reuptake mechanism, turning it into a pump instead of a vacuum. Sources note that amphetamine and related compounds (ephedrine, etc.) displace noradrenaline from the presynaptic neuron and do not act as reuptake inhibitors as referenced above.

The increased flow of dopamine and norepinephrine into the extraneuronal space causes the patients' brain, as one psychiatrist explains, to experience a more intense level of concentration, causing an increased ability to focus for extended periods of time, and a heightened interest in performing focus based tasks.

Though rare, it is possible for Adderall to cause psychotic episodes at recommended doses in patients with a history of psychosis.

Some patients feel they are less creative while taking Adderall, while others report that it can aid in creative work. The famous Beat generation writer Jack Kerouac, for instance, is said to have written much of his classic On The Road in a span of three weeks, aided by Amphetamine (an active ingredient in Adderall) from Benzedrine inhalers; country music star Johnny Cash had a long period of amphetamine use in the 1960s; and mathematician Paul ErdQs was noted for habitual use of prescription amphetamine throughout the final decades of his life; Smile was written by Brian Wilson and Van Dyke Parks with heavy

amphetamine use, among others. All of these probably knew the drug by its common name, speed.

Double-blind, placebo-controlled studies of dextroamphetamine in normal subjects have shown significant performance increases on cognitive tasks and decreased reaction time.

Clinical trials establishing the long term effectiveness of Adderall have not been conducted. Controlled studies have not occurred for children on Adderall for a period exceeding three weeks. Also, reviews of effectiveness for adolescents or adults on the medication for longer then four weeks have not been evaluated. Several studies on pregnant rodents have shown that exposure to amphetamines in utero or postnatal can lead to neurological damage and variance in behavior. While more controlled studies on pregnant women taking Adderall are needed, amphetamines have been shown to pass through into breast milk. Because of this, mothers taking medications containing amphetamines are advised to avoid nursing during their course of treatment.

Side effects

Common side effects of Adderall include:

- Increased heart rate
- Insomnia
- Anorexia (loss of appetite)
- Vertigo
- Headache
- Diarrhea
- Sweating
- Sexual dysfunction (impotence or changes in sex drive)
- Dry Mouth
- Irritability
- Tremor
- Euphoria

Less common side effects

- Upset stomach
- Nervousness
- Mydriasis
- Bruxism (teeth grinding)
- Formication (in excessive doses [3])
- Urinary retention
- Pyrexia
- Tachycardia
- Tics
- Urticaria
- Increased Urination (Your body's way of combating hypertension[citation

needed]])
Blunted affect
Detachment from reality

Rare side effects

- Phonic tics
- high blood pressure

- hallucinations

- Tourette's syndrome
cardiomyopathy

Contraindications

Using any Amphetamine, (including Adderall, Methamphetamine or Ecstasy) within 1-2 weeks of taking a monoamine oxidase inhibitor (MAOI) (an archaic branch of the antidepressant class) can cause a potentially fatal condition known as serotonin syndrome.

Performance-enhancing use

Because Adderall uses amphetamine stimulants to help the user concentrate for extended periods of time, many students today request Adderall from doctors in order to use it as a study aid. Thus, it is increasingly popular on college campuses. The largest benefit to students, however, is Adderall's ability to give students the power to focus on and learn what would usually be uninteresting material. Because of the appetite-suppressing properties of amphetamines, it is also sought after by those wishing to lose weight. Another less common use for students is to take Adderall before or during a night of heavy drinking in order to remain alert and active despite being intoxicated.

To add further insight to Adderall use among college students, research done by the National Institute of Drug Abuse (NIDA) shows the more competitive the college, the higher the incidence of stimulant use. An article published stated the findings of a nationwide survey of thousands of college students. The findings of this past April 2006 survey shows 5.9% use rates among the more competitive campuses, compared to 1.3% use rates among less competitive campuses. Breaking down the use pattern even further, this same sample done by NIDA reveals whites were more likely to use stimulants compared to African Americans and Asians, at rates of 4.9%, 1.6%, and 1.3% respectively. Further, students with lower grade point averages of B's or below use stimulants at a rate of 5.2%, compared to students earning B+ or above who use this medication at rates of only 3.3%. This research also specifically identified that students involved in sororities or fraternities use stimulants at a much higher rate of 8.6% compared to nonmembers who reported use at rates of only 3.3% (Whitten, 6).

In addition to the physiological risks posed by using Adderall as a way to enhance performance, the use of prescription stimulants has a direct correlation to higher levels of smoking cigarettes, binge drinking, risky behavior including driving while under the influence of drugs and the use of marijuana, ecstasy and cocaine. For example, the NIDA survey respondents revealed the likelihood that a stimulant user used cocaine in the past year was twenty times that of a non-user. Similarly, they reported being five times as likely to drive drunk (Whitten, 6).

Another major concern about the use of Adderall among college students is the psychological dependence that causes students to lose faith in their own ability to perform well and the dependence on the advantageous effects of stimulant medication. Jackie Kurta, an Alcohol and Drug Specialist at UC Santa Barbara's Student Heath Services states, "Students start out taking study drugs one time to study. The drugs work so well that the students begin to lose confidence in their own abilities to study without them," (Hirschey).

On the street, Adderall is sold illegally for $3 to $10 a pill (pills ranging from 5 to 35 mg) Slang terms for Adderall are: "slack", "zing", "fatty addy", "Blue Spanish Fly", "a.d.", "study buddies", "ralls", "headlight through fog," "smart pills", "beenies", "amps", "a-bombs", "cactus jacks", "uppies", "Freud's Love", "blasters", "corvettes" (refering to the 35 mg pill), "Duke Ellingtons", "addies", "poopy," "blue buddies", "Blue Betties", "orange tic-tacs", "the blue dutchman", "candy", "A candy", "blue boy," "nig nigs", "jollies", "smurphs", "rinky dink," "diet coke", "Thrash" by some skateboarders, "Davies"(for their founder, Dave Herrington), "team blue", "derallo," "the A train", "A+" in reference to its stimulant effect (Ambien is often referred to as "A-", the reverse effect of Adderall), and in some regions of the U.S., "railguns" and "that'da boy(s)" (from noted increase in productivity). On some college campuses taking Adderall is known as "taking the A train" or "getting some vitamin A", most likely inspired by the song "Take The A Train" by Duke Ellington. The 5 and 10 mg doses are also known in the northwest as "BBs",] which is short for "Blueberries", named for their blue color. Heavier users tend to use the term "GBs", which is short for "goof balls". Some Adderall users crush and inhale the 5 and 10 mg pills to experience a stronger "rush" and a more rapid onset of the drug's effects. This has led to the term "smurf snot," used to describe how the pills color one's mucus blue.

Aside from being used by college students as a study aide, Adderall has been used as an off label drug for weight loss. Adderall's side effect of weight loss and appetite suppression is a desired result for those trying to lose weight. It is administered as part of a "cocktail" of other off label prescription drugs that have side effects used to treat obesity. There have not been any scientific studies performed to evaluate the effectiveness of this form of treatment and is viewed a very risky and potentially dangerous way to shed pounds.

History/How it works

Adderall, formulated in the early 1990's, is the newest and most popular drug on the market for the treatment of ADHD. Due to the composure of Adderall, the four salts listed beforehand, it is superior to any other ADHD drug that has been created and used in the past. With Adderall, as opposed to drugs like Ritalin and Dexedrine, there are hardly any issues with withdraw that were clearly apparent with ADHD drugs in the past. Not only is Adderall considered a smoother ADHD drug than any other, but because of its potency there is no

need for doses to be taken throughout the day as was the case with previous drugs for treatment. Results yield that Adderall is just as effective, if not better, in treating the symptoms of ADHD in children as well as adults (about 60-70% improvement).

ADHD is a diagnosis of what is believed to be a part of the brain that insufficiently regulates brain chemicals. This irregularity causes decrease in efficiency which leads to the symptoms that define ADHD. The way Adderall works is by stimulating these areas of the brain that are considered to be working and regulating improperly. The proper dose of Adderall boosts this part of the brain to perform and function at the normal level, reverting one to normal behavior. Normal behavior is attached to a person who can maintain focus, promote calmness, and control their impulsivity.

Government warnings

On February 9, 2005, Health Canada suspended all sales of Adderall XR after data collected by manufacturer Shire Pharmaceuticals linked the drug to 12 sudden deaths in American children between the years 1999 to 2003. Further research, however, found little data suggesting use of Adderall resulted in an increased risk of cardiac defect. Of the twelve sudden deaths positively linked to pediatric Adderall users during the four year period, five had known pre-existing cardiac conditions, one died after strenuous exercise in 110 degree heat and two had levels suggestive of an overdose. Given the more than 37,000,000 prescriptions for Adderall filled during the four years, the US Food and Drug Administration could find no increased risk of sudden death among Adderall users beyond the normal rate of the general population. In August, 2005, Health Canada followed the committee report of three independent physicians and lifted the ban on Adderall XR. Given that persons with AD/HD are a high risk group, it has been suggested that stimulant medications for persons with AD/HD will actually result in lower incidence of premature death.

Currently the FDA and Health Canada advise against the use of Adderall in those persons with pre-existing cardiac or mental illnesses. They also suggest against its use in persons who have a history of drug abuse.Although FDA safety advisors voted 8 to 7 to issue a Black Box Warning, the FDA's pediatric advisory committee refused to give the drug its most severe black box warning in March, 2006. A Black Box Warning regarding amphetamine abuse potential is in place, however.Manufacturers

Adderall is manufactured by Catalytica Pharmaceuticals Inc. of Greenville, North Carolina and is distributed by Shire Pharmaceuticals. Generic equivalents (known to pharmacists as "amphetamine salts," "mixed amphetamines," or simply "amphetamines," inter alia) are also distributed in the United States by Barr Pharmaceuticals, Mallinckrodt Pharmaceuticals, Eon Labs and Ranbaxy Laboratories.

See also

- Amphetamine
- methamphetamine
- methylphenidate

Benzedrine

Benzedrine is the trade name of the racemic variant of Amphetamine (dl-amphetamine). It was marketed under this brandname in the USA by Smith, Kline and French in the form of inhalers, starting in 1928. Benzedrine was used to enlarge nasal and bronchial passages and it is closely related to other stimulants produced later, such as Dexedrine (d-amphetamine) and methamphetamine.

Early users of the Benzedrine inhaler discovered that it had a euphoric stimulant effect, resulting in it being one of the earliest synthetic stimulants to be widely used for recreational (i.e., non-medical) purposes. Even though this drug was intended for inhalation, many people abused it by cracking the container open and swallowing the paper strip inside, which was covered in Benzedrine. The strips were often rolled into small balls and swallowed, or taken with coffee or alcohol. The drug was often referred to as "Bennies" by users and in literature.

Because of the stimulant side effect, physicians discovered that amphetamine could also be used to treat narcolepsy. This led to the production of Benzedrine in tablet form.

In the 1940s and 1950s reports began to emerge about the abuse of Benzedrine inhalers, and in 1949, doctors began to move away from prescribing Benzedrine as a bronchodilator and appetite suppressant. In 1959, the FDA made it a prescription drug in the United States.

When Benzedrine became a controlled substance, it was replaced by a less potent stimulant drug, Propylhexedrine (also known as Hexahydromethamphetamine). Propylhexedrine was also manufactured by Smith, Kline and French and was marketed under the name Benzedrex. Although Benzedrex is not as potent as Benzedrine, it still has the potential for abuse and has been the cause of death by intravenous use. The Benzedrex inhaler is still available today, but is no longer manufactured by Smith, Kline and French.

Benzedrine should not be confused with the fundamentally different substance Benzphetamine.

Influence

- Benzedrine and derived amphetamines were used as a stimulant for armed forces in World War II and Vietnam.
- This drug was very popular with the beat generation and its influence can be seen in the literature and biographies of William S. Burroughs, Jack Kerouac and Allen Ginsberg. Also, a famous user was the prolific mathematician Paul Erdös, who spent much of his restless life on psychostimulants. An article of November 1987, published in the Atlantic Monthly profiled Erdös and discussed his Benzedrine habit. Erdös said to writer Paul Hoffman that he had liked the article "...except for one thing...You shouldn't have mentioned the stuff about Benzedrine. It's not that you got it wrong. It's just that I don't want kids who are thinking about going into mathematics to think that they have to take drugs to succeed."

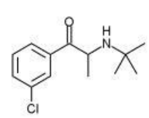
- Benzedrine is also prevalent in the James Bond novels by Ian Fleming. In the first novel, Casino Royale, the villain Le Chiffre inhales benzedrine during a battle of wills over a game of Baccarat with 007, earning himself the description, "filthy brute", from an American lady at the table next to Bond. In the novel Live and Let Die, Bond himself eats a benzedrine tablet before going underwater to infiltrate Mr. Big's lair. Similarly, in the novel Moonraker, 007 mixes the drug with champagne before his card game with Sir Hugo Drax in order to "keep my wits about me"; according to the book, the only side effect was overconfidence. In the novel Thunderball, rogue pilot Giuseppe Petacchi consumes two tablets while flying the British Vulcan bomber he has hijacked. This drug use has never featured in the film adaptations, until Casino Royale (2006 film), in which Le Chiffre uses a platinum inhaler, ostensibly for his asthma.
- Benzedrine is mentioned in the lyrics of the R.E.M. song "What's the Frequency, Kenneth?". The band later recorded a song with William S. Burroughs, whose late wife Joan was a notorious user of the drug.
- It is also mentioned in the song popularized by Fred Astaire known as "On the Beam."
- Former Beach Boy Brian Wilson claims that many of the songs on his album Smile were written while the lyricist Van Dyke Parks was under the influence of Benzedrine.
- The Beatles have said that in their early days in Hamburg, Germany, they used Benzedrine quite often in order to play several concerts a night without getting sleepy.
- In the novel Last Exit to Brooklyn by Hubert Selby Jr., the character Georgette, a transvestite, grapples with an addiction to Benzedrine in the face of her abusive brother and unrequited lust for a local drunk, Vinnie.
- Progressive house DJ duo, Deep Dish, opened their 2005 album George Is On with an intro track that states, "No stopping for benzedrine, no stopping for rock 'n roll stars".
- In Robert Harris's novel Enigma, Benzedrine is taken by the cryptanalysts of Bletchley Park in order to keep them awake and alert during shifts stretching over several days.
- Benzedrine was given to Judy Garland at a young age to help with her weight. She became dependent on the drug for the rest of her life. In the classic 1971 cult movie Vanishing Point, the main character Kowalski takes "Bennies" before undertaking his reckless drive through the Southwestern USA.
- Benzedrine is the preferred drug of choice amongst the flawed characters which make up the noir fiction of James Ellroy, who himself has confessed a past addiction to the drug.
- In Alice Sebold's novel The Lovely Bones, a mother and grandmother argue about whether Susie Salmon is - at fourteen - too young for benzedrine, her grandmother's "own personal savior."

- The song "Wet Sand" by Red Hot Chili Peppers contains the lyrics "The travesties that we have seen, are treating me like benzedrine".
- The song "Oh Marie" by Sheryl Crow, on her self-titled album released in 1996, contains the lyric "She's on magazines and Benzedrine and vodka."
- In the British Sitcom Fawlty Towers, during the episode entitled "The Psychiatrist", Sybil Fawlty (Prunella Scales) tells Basil Fawlty (John Cleese) that he is "spitting poison at them like some benzedrine puff-adder."
- In F. Scott Fitzgerald's unfinished final novel, The Last Tycoon, main character Monroe Stahr takes benzedrine before a date.
- In Joyce Carol Oates' Novel Blonde, a fictionalized version of Marilyn Monroe's life, Marilyn is said to have used Benzedrine "sparingly: to 'provide quick and valuable energy,' sorely needed by an exhausted actress" (418).
- The classic anime Akira opens with a character ordering benzedrine at a bar, with the well-known line "Red bennies. Three of 'em".
- Harry "The Hipster" Gibson had a novelty hit in 1944 with the song, "Who Put The Benzedrine In Mrs. Murphy's Ovaltine?"
- In addition to his addiction to heroin, the great jazz alto saxophonist Charlie "Bird" Parker, Jr. often took Benzedrine in tablet form, dissolved in cups of hot coffee. As a result, Parker often did not sleep for days at a time, and friends noted that he was always moving, "24/7".
- Jerry Reed and others have recorded a truck-driving song called "Caffeine, Nicotine, Benzedrine (and wish me luck)."
- Many truck driving songs, including "Six Days on the Road" and "Midnight Hauler," refer to "whites" which are the tablet form of benzedrine.

See also

- Amphetamine
- Adderall

Bupropion



Systematic (IUPAC) name

(±)-1-(3-chlorophenyl)-2-[(1,1-dimethylethyl)amino]-1-propanone

Identifiers

CAS number 34841-39-9

ATC code N07**BA02**

PubChem 444

DrugBank APRD00621

Chemical data

Formula $C_{13}H_{18}NClO$

Mol. weight 239.74 g/mol

Pharmacokinetic data

Bioavailability 5 to 20% in animals; no studies in humans

Metabolism Hepatic

Half life 20 hours

Excretion Renal (87%), fecal (10%)

Therapeutic considerations

Pregnancy cat. $B_{(US)}$

Legal status -only(US)

Routes Oral

Bupropion (or *amfebutamone*, brand names *Wellbutrin* and *Zyban*) is an antidepressant of the aminoketone class, chemically unrelated to tricyclics or selective serotonin reuptake inhibitors (SSRIs). It is similar in structure to the stimulant cathinone, and to phenethylamines in general. It is a chemical derivative of diethylpropion, an Amphetamine-like substance used as an anorectic. Bupropion is both a dopamine reuptake inhibitor and a norepinephrine reuptake inhibitor. It is often used as a smoking cessation aid.

International/alternate trade names include Odranal (Colombia), Quomen (Thailand), Well (Korea), Zyban LP (France), Zyban Sustained Release (Australia)

History

Bupropion was first synthesized by Burroughs Research in 1966, and patented by Burroughs-Wellcome (later Glaxo-Wellcome, and, as of 2000, GlaxoSmithKline) in 1974. It was approved by the Food and Drug Administration (FDA) as an antidepressant in 1989 and marketed under the name *Wellbutrin*, but clinical trials indicated that incidence of seizure was two to four times greater than other antidepressants and the drug was quickly pulled

from the market. It was subsequently discovered that reducing the dose by about half greatly reduced the risk of seizures.

Glaxo then developed a sustained-release (SR) version of Wellbutrin which releases bupropion at a slower rate. The SR formulation is taken twice a day, in order to further decrease the possibility of adverse side effects and seizures. It is also available in generic form (Bupropion SR). Extended Release bupropion, Wellbutrin XL, is the most recent formulation of bupropion and is taken orally once a day. With this altered mechanism of delivery and reduced dosing, incidence of seizures is comparable to, and in some cases lower than, that of other antidepressants. Patients using Bupropion should still be checked for pre-disposing factors that might lead to a lower than normal seizure threshold. It is also important to check for other medications the patient might be using which might also work to lower the seizure threshold.

In 1997, bupropion (as bupropion hydrochloride) was approved by the FDA for use as a smoking cessation aid. Glaxo subsequently marketed the drug under the name *Zyban* to help people stop smoking tobacco by reducing the severity of nicotine cravings and addiction/withdrawal symptoms. It can be used in combination with nicotine replacement therapies. Bupropion treatment course lasts for seven to twelve weeks, with the patient halting the use of tobacco around ten days into the course.

Bupropion is also being investigated for several other disorders including overweight or obesity, attention-deficit hyperactivity disorder, restless legs syndrome and a possible treatment for increasing sexual functioning in some women. In late 2006, Wellbutrin XL was approved for use by the FDA as treatment for seasonal affective disorder.

GlaxoSmithKline's exclusivity patent ended in early 2004. Prior to this, there were several patent suits, the biggest of which involved the pharmaceutical company called Andrx in 1999. After an intitial dismissal of the case in 2003, several court appeals by Glaxo resulted in the refiling of the case. The suit is still pending.[1]

Mode of action

Bupropion is a selective catecholamine (norepinephrine and dopamine) reuptake inhibitor. It has only a small effect on serotonin reuptake. It does not inhibit MAO. The antidepressant effect of bupropion is considered to be mediated by its dopaminergic and noradrenergic action. Bupropion has also been shown to act as a competitive $\pm3^{2}4$ nicotinic antagonist, the $\pm3^{2}4$-antagonism has been shown to interrupt addiction in studies of other drugs such as ibogaine. This $\pm3^{2}4$-antagonism correlates quite well with the observed effect of interrupting addiction.

Pharmacokinetics

Bupropion is metabolised in the liver. It has at least three active metabolites: hydroxybupropion, threohydrobupropion and erythrohydrobupropion. These active metabolites are further metabolised to inactive metabolites and eliminated through excretion into the urine. The half-life of bupropion is 20 hours, as is hydroxybupropion's. Threohydrobupropion's half-life is 37 hours and erythrohydrobupropion's is 33 hours.

Chronic hepatotoxicity in animals

In rats receiving large doses of bupropion chronically, there was an increase in incidence of hepatic hyperplastic nodules and hepatocellular hypertrophy. In dogs receiving large doses of bupropion chronically, various histologic changes were seen in the liver, and laboratory tests suggesting mild hepatocellular injury were noted.

Contraindications

- Epilepsy and other conditions that lower the seizure threshold (alcohol withdrawal, active brain tumors etc.)
- Concomitant treatment with MAO inhibitors. When switching medications it is important that there be a short period of about two weeks between the medications in order to reduce risk of complications that might lead to things such as a decrease in seizure threshold.
- Caution with the concomitant use of sympathomimetic drugs (e.g. ephedrine)
- Active liver damage (e.g. cirrhosis)
- Anorexia nervosa and bulimia which might lead the patient to have a decreased seizure threshold
- Severe kidney disease
- Severe hypertension
- Anxiety disorders (caution), agitated patients
- Pediatric patients (see below)
- Use considerable caution in treating patients where suicide may be a risk (risk is no higher than any other antidepressant)

Side effects

Common side effects include dry mouth, tremors, anxiety, loss of appetite, agitation, dizziness, headache, excessive sweating such as night sweats, increased risk of seizure (Its most controversial side effect, found in 4/1000 during trials), aggressiveness, and both initial and terminal insomnia. Activation of mania and psychosis have both been encountered. Some patients may also require less than the normal dosing which usually starts at around 150 mg for the first few weeks and is then switched to the normal 300 mg dosage; these patients may be kept on the 150 mg regimen.

Suicidal thoughts and attempts have been reported in children and adolescents. Reports of increasing suicidal thoughts have occurred.

Scattered abnormalities of liver function tests are noted, without evidence of hepatotoxicity. Cases of significant liver damage with or without jaundice (icterus) have been seen rarely. In a German database covering side effects, five cases of pancreatitis with elevations of serum-amylase and lipase as well as clinical symptoms (e.g. abdominal pain, anorexia), reversible after termination of bupropion, have been reported. Currently, it is unclear whether preexisting alcohol abuse or dependence might predispose patients to develop pancreatitis.

Infrequently, dose-dependent hypertension is noted. Single cases of myocardial infarction (heart attack) have been noted, but the causal association to the use of bupropion is currently unknown.

The development of mild to moderate skin rashes associated with sensitivity to dye components within the pill coating. This can often be alleviated by simply prescribing a different color pill and consequently, changing the dosage.

Few cases of the urological emergency priapism (painful erection) have been seen. Immediate treatment is necessary, because the untreated patient may totally lose his ability to have erections.

Interactions

Quite a great number of drugs show clinically significant interactions with bupropion. This may be due to interactions with drugs that are metabolized by CYP2D6 as bupropion inhibits CYP2D6 activity. However, bupropion is not metabolized by CYP2D6.

Manufacturer studies have also indicated that bupropion is primarily metabolized to hydroxybupropion by the CYP2B6 isoenzyme. Theoretically, drug interactions could occur between bupropion and substrates or inhibitors of CYP2B6 (e.g. orphenadrine, thiotepa, or cyclophosphamide).

Bupropion is known to lower the seizure threshold. Bupropion, in combination with other medications, has been suspected to induce seizures in some patients with no prior record of seizure activity.[1] While this is not a common side-effect, a growing number of cases world wide validate the need for consideration. It is not uncommon for patients to receive treatment with other antidepressant and/or atypical antipsychotic medications in combination with bupropion. For this reason, care should be taken when prescribing bupropion with other medications prone to lower the seizure threshold. Bupropion has also been known to produce seizures in combination with non-prescription (recreational) drugs such as cocaine, and alcohol. Study the packing insert carefully and ask your prescribing physician about possible interactions.

Abuse liability

In animal studies and small studies with persons having experience with the use of Amphetamine or cocaine, bupropion caused drug-seeking behaviour (animal experiments) and was recognized as an amphetamine-like drug by humans. In a scale ranging from placebo on the lower side to benzedrine, it was given an intermediate score indicating moderate likelihood of abuse. In clinical practice, bupropion has been shown that the dose required for significant abuse would cause seizures in most patients. Abuse has not become a significant problem in clinical usage, but the drug should be given with caution to patients with a history of drug or alcohol abuse or dependence.

Dosage

- Depression: the target dosage is 300 mg daily, starting with 150 mg in the first few days. If indicated and directed by physician, the dosage may be increased to a maximum of 450 mg daily.
- Tobacco withdrawal: 150 mg initially, may be increased to 300 mg if indicated and directed by physician. In patients also receiving insulin, sympathomimetic anorectical drugs, or antimalaria agents, the daily dose of bupropion should not exceed 150 mg.

Dose forms

Brand and generic pills are available in three forms: immediate release, sustained release (SR), and extended release (XL, ER).

Brand Name	Dosage	Color
Wellbutrin	75 mg	yellow-gold
Wellbutrin	100 mg	red
Wellbutrin SR	100 mg	blue
Wellbutrin SR	150 mg	purple
Wellbutrin SR	200 mg	pink
Wellbutrin XL	150 mg	white
Wellbutrin XL	300 mg	white
Zyban SR	150 mg	purple

Overdosage

GlaxoSmithKline has reported that overdoses of up to 30 g or more of Wellbutrin (bupropion) had resulted in seizure in about one third of all cases. Hallucinations, loss of consciousness, sinus tachycardia, and ECG changes such as conduction disturbances or arrhythmias were reported as other serious reactions of overdoses of bupropion alone. Multiple overdoses including bupropion had resulted in fever, rhabdomyolysis, stupor, hypotension, coma, muscle rigidity, and respiratory failure.[2]

Additional warnings

May cause false-positive for amphetamine

Bupropion contains a similar pharmacological structure to that of amphetamines. In most cases prescription medications that contain bupropion (Wellbutrin, Zyban) will produce a positive result for amphetamine abuse.

Use in pediatric patients

Bupropion has been shown to increase the incidence of suicidal thoughts and attempts in children and adolescents with depression. When treating major depressive disorder in this group of patients, clinical benefits should be weighed carefully against therapeutic hazards. Usually, bupropion is not indicated for pediatric patients under age 18.[3]

Potential indications of bipolar and schizoaffective disorder

The effects of bupropion in treating eleven patients with bipolar or schizoaffective disorder were examined in an open trial.[4] Most patients had been intolerant of or showed minimal to moderate improvement on lithium, neuroleptics, antidepressants, or a combination of these drugs. All patients were maintained on bupropion alone or bupropion in combination with low-dose neuroleptics or anxiolytics for one year or more, with little or no relapse and few side effects. Although these results are encouraging, additional larger studies need to be conducted to confirm this indication.

Alleged risks with certain treatments

In the UK, more than 7,000 reports of potential hazardous side effects have been collected. There have been 44 reports of suspected adverse reactions where there was a fatal outcome while taking Zyban. In reviewing these cases the MHRA state that in the majority of cases the individual's underlying condition may provide an alternative explanation.[5] More than two thirds of reported deaths were from cardio-vascular or cerebro-vascular causes. A case-series analysis showed increased risk of seizure in the population taking bupropion, but no increase in the risk of sudden death.[6] At least 107 cases of serious side effects have been reported in Germany. Wellbutrin is also banned or restricted from use in several countries.

In the UK, bupropion should only be prescribed as an aid in quitting smoking to smokers who have committed to a definite quit date and a prescription will not last more than 4 weeks after this target date. NICE has issued guidance to the effect that if the attempt to quit is unsuccessful the NHS will not provide funding for a further course, for at least 6 months.

In some countries bupropion is approved only as a smoking cessation aid and not for treatment of depression.

Studies of juveniles with depression

A large study gathered the results of twenty-four studies of juveniles with depression. Patients were to take either a placebo (sugar pill) or an antidepressant (SSRIs and others, including bupropion) for one to four months. According to the results, nobody committed suicide in these studies, although two out of every hundred patients became suicidal on a placebo and four out of every hundred become suicidal on antidepressants. Results indicated that the risks of suicidal actions become high for some juveniles. These kinds of juveniles may include patients with:[2]

- Bipolar illness, previously known as manic-depressive illness
- A family history of bipolar illness
- A personal or family history of attempting or committing suicide

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Ephedrine

Systematic (IUPAC) name

(1R,2S)-2-(methylamino)-1-phenylpropan-1-ol

Identifiers

CAS number rn=1" href="http://www.nlm.nih.gov/cgi/mesh/2006/MB_cgi?term=299-42-3&rn=1"> 299-42-3

ATC code R01**AA03** R03**CA02** S01**FB02**

PubChem 5032

DrugBank nil

Chemical data

Formula $C_{10}H_{15}NO$

Mol. weight 165.23

Pharmacokinetic data

Bioavailability **85%**

Metabolism minimal hepatic

Half life 3–6 hours

Excretion 22-99% renal

Therapeutic considerations

Pregnancy cat. $A_{(AU)}$ $A_{(US)}$

Legal status S4(AU) Schedule VI(CA) P(UK)

Routes oral, IV, IM, SC

Ephedrine (EPH) is a sympathomimetic amine similar in structure to the synthetic derivatives Amphetamine and methamphetamine. Ephedrine is commonly used as a stimulant, appetite suppressant, concentration aid, decongestant and to treat hypotension associated with regional anaesthesia. Chemically, it is an alkaloid derived from various plants in the genus Ephedra (family Ephedraceae). It is most usually marketed in the *hydrochloride* and *sulfate* forms.

In traditional Chinese medicine, the herb ma huang (Ephedra sinica) contains ephedrine as its principal active constituent. The same is true of other herbal products containing extracts from Ephedra species. Nagayoshi Nagai was the first one to isolate ephedrine from Ephedra vulgaris in 1885. The substance called soma mentioned in old Hindu books such as the Rig Veda, may have been ephedra extract.

Chemistry

Ephedrine exhibits optical isomerism and has two chiral centres. By convention the enantiomers with opposite stereochemistry around the chiral centres are designated ephedrine, while pseudoephedrine has same stereochemistry around the chiral carbons. That is, (1R,2R)- and (1S,2S)-enantiomers are designated pseudoephedrine; while (1R,2S)- and (1S,2R)-enantiomers are designated ephedrine.

The isomer which is marketed is (-)-(1R,2S)-ephedrine. [1]

As with other phenylethylamines, it is also somewhat chemically similar to methamphetamine, although the amphetamines are more potent and have additional biological effects.

Ephedrine may also be referred to as: (±R)-±-[(1S)-1-(methylamino)ethyl]benzenemethanol, ±-[1-(methylamino)ethyl]benzyl alcohol, or L-erythro-2-(methylamino)-1-phenylpropan-1-ol. Ephedrine hydrochloride has a melting point of 187-188°C. [2]

Mode of action

Ephedrine is a sympathomimetic amine - that is, its principal mechanism of action relies on its indirect action on the adrenergic receptor system, which is part of the sympathetic nervous system or SNS. Whilst it may have weak agonist activity at ±- and ^{2}-adrenergic receptors, the principal mechanism is to displace noradrenaline from storage vesicles in presynaptic neurons. The displaced noradrenaline is released into the neuronal synapse where it is free to activate the postsynaptic adrenergic receptors.

Ephedrine's mechanism of action on neurotransmission in the brain is wide. Its action as an agonist at most major norepinephrine receptors and its ability to induce moderate stimulation of the release of both dopamine and to a lesser extent, serotonin, is presumed to have a major role in its mechanism of action.

Because of ephedrine's ability to potentiate dopamine neurotransmission it is thought to have addictive properties by some researchers.

While ephedrine's role in the serotonin system is less understood there is preliminary documentation of clinically significant agonism at excitory serotonin receptors, perhaps as a downstream response to the large release of norepinephrine in the nucleus accumbens (commonly referred to as the "pleasure center" of the brain). In mice, stereotypical behaviour was both easily induced by administration of ephedrine and it's primary alkaloids and reversed when serotonin antagonists were administered.

Clinical use

Ephedrine was once widely used as a topical decongestant and as a bronchodilator in the treatment for asthma. It continues to be used for these indications, although its popularity is waning due to the availability of more effective agents for these indications which exhibit fewer adverse effects [3]. The role in nasal congestion has largely been replaced by more potent ±-adrenergic receptor agonists (e.g. oxymetazoline). Similarly the role of ephedrine in asthma has been almost entirely replaced by ^{2}***2***-adrenergic receptor agonists (e.g. salbutamol). Ephedrine continues to be used intravenously in the reversal of hypotension from spinal/epidural anaesthesia [3]. It is also used in other hypotensive states, including overdose with ganglionic blocking agents, antiadrenergic agents, or other medications that lower blood pressure [4]. It can be used in narcolepsy and nocturnal enuresis.

In traditional Chinese medicine, ephedrine has been used in the treatment of asthma and bronchitis for centuries [5].

An ECA stack is a component found in thermogenic weight loss pills, composed of ephedrine, caffeine and aspirin working to speed up the metabolism and thus cause food energy to burn faster. The ECA stack is a popular supplement taken by body builders before workouts due to the increased amount of energy and alertness.

For many years, the US Coast Guard recommended ephedrine together with an equal 25 mg dose of promethazine to its sailors to combat seasickness. Promethazine manages nausea and ephedrine fights the ensuing drowsiness. Commonly referred to as the Coast Guard cocktail, ephedrine may still be available for prescription for this purpose.

Adverse effects

Adverse drug reactions (ADRs) are more common with systemic administration (e.g. injection or oral administration) compared to topical administration (e.g. nasal instillations). ADRs associated with ephedrine therapy include [3]:

- Cardiovascular: tachycardia, cardiac arrhythmias, angina pain, vasoconstriction with hypertension

Dermatological: flushing,acne vulgaris
Gastrointestinal: nausea, appetite loss, anorexia
Genitourinary: increased urine output due to increased blood flow
Nervous system:restlessness, confusion, insomnia, mild euphoria, mania/hallucinations (rare except in previously existing psychiatric conditions), delusions, formication (may be possible, but lacks documented evidence) paranoia, hostility, confusion, panic, stereotypical behaviour ('obsessive compulsive' or repetitive tasks such as cleaning, grooming, organizing items arbitrarily) agitation
Respiratory: dyspnea, pulmonary edema
Miscellaneous: dizziness, headache, tremor, hyperglycemic reactions

The approved maximum daily dosage of ephedrine for use as a bronchodilator is 150mg, as specified on the packaging of the bronchodilator and expectorant combination, Bronkaid, made by Bayer pharmaceuticals.

Overdose can lead to death, although the approved dose is not likely to cause severe reactions when used as directed.

Ephedrine can also lead to damage of the brain receptors over a period of large usage this is because of its constant action on the nuerochemicals. It also leads to high increase in blood pressure which over time can lead to damage in the blood vesasals.

Contraindications

Ephedrine should not be used in conjunction with certain antidepressants, namely SNRIs (Selective norepinephrine re-uptake inhibitors), as this increases the risk of the above symptoms due to excessive serum levels of norepinephrine.

Wellbutrin is an example of an antidepressant with an amphetamine-like structure similar to ephedrine. It has a similar action but also releases serotonin from presynaptic clefts. It should not be used with ephedrine as it may increase the liklihood of the above side effects.

Ephedrine should be used in caution in patients with inadequate fluid replacement, impaired adrenal function, hypoxia, hypercapnia, acidosis, hypertension, hyperthyroidism, prostatic hypertrophy, diabetes mellitus, cardiovascular disease, during delivery if maternal BP > 130/80 mmHg, and lactation.[6]

Contraindications for the use of ephedrine include: closed angle glaucoma, phaeochromocytoma, asymmetric septal hypertrophy (idiopathic hypertrophic subaortic stenosis), concomitant or recent (previous 14 days) monoamine oxidase inhibitor (MAOI) therapy, general anaesthesia with halogenated hydrocarbons (particularly cyclopropane or halothane), tachyarrhythmias or ventricular fibrillation, hypersensitivity to ephedrine or

other stimulants, and psychoneurosis (bipolar disorder, severe depression, obsessive compulsive disorder, etc.)

Ephedrine should NOT be used at any time during pregnancy unless specifically indicated by a qualified physician and ONLY when other options are unavailable.[6.

Recreational and illicit use

Anecdotal reports have suggested that ephedrine helps studying, thinking, or concentrating to a greater extent than caffeine. Some students and some white-collar workers have used ephedrine (or Ephedra-containing herbal supplements) for this purpose, as well as some professional athletes and weightlifters. It is common for many athletes to use stimulants while exercising. Such misuse of ephedrine has been associated with stimulant dependence, as well as deaths from heatstroke in athletes and circulatory problems such as aortic aneurysm in weightlifters.

As a phenylethylamine, ephedrine has a similar chemical structure to Amphetamine. Ephedrine can be used in the synthesis of methamphetamine by chemical reduction; this has made ephedrine a highly sought-after chemical precursor in the illicit manufacture of methamphetamine. The most popular method for reducing ephedrine to methamphetamine is similar to the Birch reduction, in that it uses anhydrous ammonia and lithium metal in the reaction. The second most popular method uses red phosphorus, iodine, and ephedrine in the reaction.

Through oxidation, ephedrine can be easily synthesized into methcathinone. Ephedrine is listed as a Table I precursor under the United Nations Convention Against Illicit Traffic in Narcotic Drugs and Psychotropic Substances [7].

Ephedrine has been reported to cause both physical and psychological dependence after excessive long-term use. This is particularly true with oral forms of ephedrine, since parenteral administration is unlikely to occur over long periods [6].

Neurotoxicity of Ephedrine

As a sympathomimetic agent similar in structure and activity to amphetamines, there has been a dispute over whether ephedrine produces some of the same neurodegenerative effects. It has been shown clinically that certain amphetamines (namely (d)-amphetamine and (d)-methamphetamine) can cause varying levels of long-term dopamine depletion in dopamine-rich brain and nervous centers such as the putamen and the basal ganglia.

Several studies have recently compared the quantities of such neurotransmitters as serotonin, dopamine, glutamate, and adrenaline after concurrent administration of ephedrine and various amphetamine-like agents. The results showed that ephedrine has a reduced neurotoxic effect on dopamine than its amphetamine counterparts.

Ephedrine increases serum dopamine levels minimally in comparison with an equivalent dose of dextroamphetamine (Adderall®). Dextromethamphetamine (Desoxyn®) raises dopamine levels dramatically (more than two times that of an equivalent dose of dextroamphetamine). This supports the general consensus that ephedrine has more of a peripheral action on the sympathetic nervous system, whereas amphetamines appear to

cross the blood brain barrier more freely and tend to have a stronger central action. The fact that dopamine is believed to play a major role in the addiction response has been used in recent years as justification for controlling the distribution of dextroamphetamine and dextromethamphetamine, along with various other amphetamines.[8]

Legality in USA

Ephedrine itself has never been illegal. In 1996, the FDA proposed a regulation on ephedra (the herb from which ephedrine is obtained), which limited an ephedra dose to 8mg with no more than 24mg per day. This proposed rule was then withdrawn in 2000 because "concerns regarding the agency's basis for proposing a certain dietary ingredient level and a duration of use limit for these products." In 2004, the FDA created a ban on ephedrine alkaloids that are marketed for reasons other than asthma, colds, allergies, other disease, or traditional Asian use. Products such as VasoPro's ephedrine HCL contains Guaifenesin, which thins the mucus in the air passages and makes it easier to clear the airway, and thus is sold as a bronchodilator. On April 14th, 2005, the US Federal District Court ruled that the FDA did not have proper evidence that low dosages of ephedrine alkaloids are actually unsafe, but on August 17, 2006, the U.S. Court of Appeals for the Tenth Circuit in Denver upheld the FDA's final rule declaring all dietary supplements containing ephedrine alkaloids adulterated, and therefore illegal for marketing in the United States. Ephedrine is, however, still legal in many applications outside of as dietary supplements. However, currently purchasing is limited and records are kept of how much ephedrine is purchased, with the specifics varying from state to state. Although the FDA claims that their ruling is a result from several deaths from people taking large doses, some people believe that it is only because ephedrine is one of the key ingredients for creating crystal meth, and that is the reason the FDA limits the total quantity one can purchase.

Footnotes

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See also

- Phenethylamines
- Methamphetamine
- Soma

Methamphetamine

Systematic (IUPAC) name

(S)-N-methyl-1-phenyl-propan-2-amine

Identifiers

CAS number 537-46-2

ATC code N06**BA03**

PubChem 1206

Chemical data

Formula $C_{10}H_{15}N$

Mol. weight 149.2 g/mol

Pharmacokinetic data

Bioavailability Depends on route of administration

Metabolism Hepatic

Half life 9-15 hours[1]

Excretion Renal

Therapeutic considerations

Pregnancy cat. $C_{(US)}$

Legal status Schedule I(CA) Schedule II(US) Class A(NZ), Schedule 5(SA), Injectable:Class A, Oral: B(UK)

Routes Medical: Oral
Recreational: Oral, I.V., I.M., Insufflation, Inhalation, Suppository

Methamphetamine (sometimes referred to as methylAmphetamine or desoxyephedrine) is a psychostimulant drug used primarily for recreational purposes, but is sometimes prescribed for ADHD and narcolepsy under the brand name Desoxyn. It causes euphoria and excitement by acting directly on the brain's reward mechanisms, thus making it highly addictive. Methamphetamine rapidly enters the brain and causes a cascading release of norepinephrine and dopamine (and to a lesser extent, serotonin). Users may become obsessed or perform repetitive tasks such as cleaning, hand-washing or assembling and disassembling objects.[2] Withdrawal is characterized by increased sleeping and eating, and depression-like symptoms, often accompanied by anxiety and drug-craving.[3]

Availability and names

In the U.S., illicit methamphetamine comes in a variety of forms, with an average price of $150 per gram of pure substance.[4] Most commonly it is found as a colorless crystalline solid, sold on the street under the name *crystal meth* and a variety of other names. It is also sold as a less pure crystalline powder called crank, or in crystalline rock form. Colourful flavored pills containing methamphetamine and caffeine are known as yaba (Thai for "crazy medicine"). At its most impure, it is sold as a crumbly brown or off-white rock commonly referred to as "peanut butter crank"[5]. Methamphetamine found on the street is rarely pure, but adulterated with chemicals that were used to synthesize it. It may be diluted or "cut" with non-psychoactive substances like inositol. It may also be cut with other psychoactive substances, but the reverse is presumably more common due to its low price relative to other common drugs.

History

Methamphetamine was first synthesized from Ephedrine in Japan in 1893 by chemist Nagayoshi Nagai. In 1919, crystallized methamphetamine was synthesized by Akira Ogata via reduction of Ephedrine using red phosphorus and iodine. The related compound amphetamine was first synthesized in Germany in 1887 by Lazar Edeleanu.

One of the earliest uses of amphetamine occurred during World War II when the German military dispensed the stimulant under the trade name *Pervitin* to troops.[6] The drug was widely distributed across rank and division, from elite forces to tank crews and aircraft personnel. Chocolates dosed with methamphetamine were known as Fliegerschokolade ("flyer's chocolate") when given to pilots, or Panzerschokolade ("tanker's chocolate") when distributed to tank crews.

Adolf Hitler is rumored to have received three daily IV injections of amphetamines and steroids from his personal physician, Theodore Morell. After World War II, a massive supply of amphetamine, formerly stockpiled by the Japanese military, became available in Japan

under the street name shabu (also Philopon (pronounced ÒíÝó, or Hiropon), its tradename there.[7]) The Japanese Ministry of Health banned it in 1951, which is thought to have added to the growing yakuza activities related to illicit drug production.[8] Today, the Japanese underworld is still associated with the drug, although its use is discouraged by strong social taboos.

With the 1950s came a rise in the legal prescription of methamphetamine to the American public. According to the 1951 edition of Pharmacology and Therapeutics (by Arthur Grollman), it was to be prescribed for "narcolepsy, post-encephalitic parkinsonism, alcoholism, ... in certain depressive states... and in the treatment of obesity."

The 1960s saw the start of the significant use of clandestine manufacture to supply methamphetamine. Prior to 1983, U.S. laws prohibiting the possession of precursors and equipment for methamphetamine production were not yet in place. The recreational use of Levoamphetamine sky-rocketed in the 1980s. The December 2, 1989 edition of The Economist described San Diego, California as the "methamphetamine capital of North America."

In 1986, the U.S. government passed the Federal Controlled Substance Analogue Enforcement Act in an attempt to combat the growing use of designer drugs. In spite of this, its use expanded throughout the rural United States, especially in the Midwest and South. Growth of methamphetamine use continues into the 21st century, and many states are considering tougher legislation.

On August 8, 2005, an issue of Newsweek devoted a cover story to methamphetamine and its abuse,[9] including criticism of the Bush administration's policies regarding meth. Newsweek blamed the administration for not devoting enough resources to education about and prevention of the drug's use. The Bush administration has countered with the position that cannabis is a dangerous 'gateway drug', so prevention of cannabis use should prevent potential abusers from trying and becoming hooked on "hard" drugs such as methamphetamine.

Meanwhile, the online magazine Slate posted an article in reaction to the Newsweek article,[10] attacking Newsweek for failing to appropriately cite sources and data to back up the claim that this is a "new" problem. The topic remains controversial. The most recent figures released by the Federal government indicate that contrary to public perception, methamphetamine use has actually declined nationally in recent years.[11]

Production

Methamphetamine is most structurally similar to methcathinone and Amphetamine. In illicit production, it is commonly made by the reduction of Ephedrine or pseudoephedrine. Most of the necessary chemicals are readily available in household products or over-the-counter medicines. Synthesis is relatively simple, but most methods involve flammable and corrosive chemicals. As a result, clandestine production is often discovered due to fires caused by amateur chemists working with makeshift laboratory equipment.

Most production methods involve hydrogenation of the hydroxyl group on the ephedrine/pseudoephedrine molecule. The most common method in the United States involves red phosphorus and iodine which forms hydroiodic acid. This is a fairly dangerous process; in fact, on the Darwin Awards site, there is a story of a man who burned himself

trying to conceal these chemicals.[12] The red phosphorus production method can create phosphine gas, which is extremely toxic when inhaled. An increasingly common method utilizes a Birch reduction process, where metallic lithium is substituted for metallic sodium (due to the difficulty in obtaining metallic sodium). The Birch reduction is dangerous since the alkali metal and liquid anhydrous ammonia are both extremely reactive, and because the temperature of liquid ammonia makes it susceptible to explosive boiling when reactants are added.

Other less-common methods use other means of hydrogenation, such as hydrogen gas in the presence of a catalyst.

A completely different synthesis procedure involves creating methamphetamine by the reductive amination of phenylacetone with methylamine, both of which are currently DEA list I chemicals (as are pseudoephedrine and ephedrine). This was once the preferred method of production by motorcycle gangs in California, but DEA restrictions on the chemicals have made this an uncommon way to produce the drug today.

One of the more obvious signs of a production lab of metamphetamine in operation is the smell of a cat-urine-like odor.

When performed by individuals who are not trained chemists, methamphetamine manufacture can lead to extremely dangerous situations. For example, if the red phosphorus reaction is allowed to overheat, phosphine gas can be produced. When produced in large quantities, it usually explodes, due to autoignition from diphosphine formation caused by overheating phosphorus.

Until the early 1990s, methamphetamine for the US market was made mostly in clandestine labs run by drug traffickers in Mexico and California. These areas are still the largest producers for the U.S. market. Since then, however, authorities have discovered increasing numbers of small-scale methamphetamine labs all over the United States, mostly located in rural, suburban, or low-income areas. The Indiana state police found 1,260 labs in 2003, compared to just 6 in 1995, although this may only be a result of increased police activity.[13]

Recently, mobile and motel-based methamphetamine labs have caught the attention of both the US news media and law enforcement agencies. The labs can cause explosions and fires, as well as expose the public to hazardous chemicals. In addition to these issues, individuals who manufacture methamphetamine are often harmed by toxic gases. Many police forces have responded by creating a specialized task force educated in responding to persons involved in methamphetamine production.

The amount of methamphetamine actually contributed to the US market by small-scale labs is disputed. Large-scale labs maintained by criminal organizations continue to exist. In the United States, Drug policy critics suggest that restriction of over-the-counter medication is more politically than socially motivated, and may in fact shift the balance of supply more in favor of large criminal organizations.

Distribution

A wide variety of groups are involved in the distribution of methamphetamine, from the aforementioned prison gangs and motorcycle gangs to street gangs, traditional organized crime operations, and impromptu small networks made up of users. The government of

North Korea has been linked to the manufacture and distribution of crystal meth, and allegedly plays a role in distribution networks throughout Asia as well as those in Australia and even in North America [14]. Regardless, meth trafficking is not exclusively dominated by cartels along the lines of Colombian cocaine cartels or Pakistani heroin cartels.

Medical use

- Attention deficit hyperactivity disorder
  Narcolepsy
  Extreme obesity
  Severe depression

- Decongestant

Pharmacology

Methamphetamine is a potent central nervous system stimulant which affects neurochemical mechanisms responsible for regulating heart rate, body temperature, blood pressure, appetite, attention, mood and responses associated with alertness or alarm conditions. Methamphetamine causes the norepinephrine transporter, dopamine transporter to reverse their direction of flow. This inversion leads to a release of these transmitters from the vesicles to the cytoplasm and from the cytoplasm to the synapse, causing increased stimulation of post-synaptic receptors. Methamphetamine also indirectly prevents the reuptake of these neurotransmitters, causing them to remain in the synaptic cleft for a prolonged period. Serotonin levels are only weakly affected (ratio NE: DA = 2:1, NE:5HT = 60:1).[15] It is neurotoxic in overdose.[16]

The acute effects of the drug closely resemble the physiological and psychological effects of an

L-methamphetamine (also called levmetamfetamine and desoxyephedrine) has nasal decongestant activity and no abuse potential. This is the active ingredient in the US Vicks Inhaler.

Tolerance

As with other amphetamines, tolerance to methamphetamine is not completely understood, but known to be sufficiently complex that it cannot be explained by any single mechanism. The extent of tolerance and the rate at which it develops varies widely between individuals, and even within one individual it is highly dependant on dosage, duration of use and frequency of administration. Many cases of narcolepsy are treated with methamphetamine for years without escalating doses or any apparent loss of effect.

Short term tolerance can be caused by depleted levels of neurotransmitters within the vesicles available for release into the synaptic cleft following subsequent reuse (tachyphylaxis). Short term tolerance typically lasts 2-3 days, until neurotransmitter levels are fully replenished. Prolonged overstimulation of dopamine receptors caused by

methamphetamine may eventually cause the receptors to downregulate in order to compensate for increased levels of dopamine within the synaptic cleft.[17] To compensate, larger quantities of the drug are needed in order to achieve the same level of effects.

Side effects

The most common side effects include twitching, "jitteriness", repetitive behavior (known as "tweaking"), and jaw clenching or teeth grinding.

Methamphetamine addicts may lose their teeth abnormally fast, a condition known as "meth mouth". Similar, though far less severe symptoms have been reported in clinical use of other amphetamines, where effects are not exacerbated by a lack of oral hygiene for extended periods.[18] Like other substances which stimulate the sympathetic nervous system, methamphetamine causes decreased production of acid-fighting saliva and increased thirst, resulting in increased risk for tooth decay, especially when thirst is quenched by high-sugar drinks.[19]

Users may exhibit sexually compulsive behavior and may engage in sexual acts with one or more individuals. This sexual behavior is believed to have created a link between meth use and sexually transmitted disease (STD) transmission, especially HIV and syphilis. This caused great concern among larger gay communities, particularly those in Atlanta, Miami, Chicago, New York City, and San Francisco, leading to outreach programs and rapid growth in 12-step organizations such as Crystal Meth Anonymous.

Common side effects:[20]

- Diarrhea, nausea
- Loss of appetite, insomnia, tremor, jaw-clenching
- Agitation, compulsive fascination with repetitive tasks (Punding)
- Talkativeness, irritability, panic attacks
- Increased libido
- Dilated pupils

Side effects associated with chronic use:

- Drug craving
- Weight loss
- Withdrawal-related depression and anhedonia
- Erectile dysfunction ("Crystal cock")
- Rapid tooth decay ("meth mouth")
- Amphetamine psychosis

Side effects associated with overdose:

- Formication (sensation of flesh crawling with bugs, with possible associated compulsive picking and infecting sores "Meth Mites")
- Brain damage (Neurotoxicity)

- Paranoia, delusions, hallucinations
- Kidney damage (from Hyperkalemia)

Overdose fatalities are usually due to stroke or heart failure, but can also be caused by hyperthermia or kidney failure.

Addiction

Methamphetamine is highly addictive, particularly when injected or smoked.[21] While not life-threatening, withdrawal is often intense and, as with all addictions, relapse is common. To combat relapse, many recovering addicts attend 12 Step meetings, such as Crystal Meth Anonymous.

In an article about his son's addiction to methamphetamine, a California writer who has also experimented with the drug put it this way:

[T]his drug has a unique, horrific quality. In an interview, Stephan Jenkins, the singer in the band Third Eye Blind, said that methamphetamine makes you feel 'bright and shiny.' It also makes you paranoid, incoherent and both destructive and pathetically and relentlessly self-destructive. Then you will do unconscionable things in order to feel bright and shiny again.[22]

Former users have noted that they feel stupid or dull when they quit using methamphetamine. This is because the brain is adapting a need for methamphetamine to think faster, or at what seems to be a higher level. Individuals with ADHD may be at higher risk for addiction to methamphetamine, because the drug increases the user's ability to focus and reduces impulsivity. Because of its abuse potential, meth is not generally prescribed for ADHD unless other stimulants, such as methylphenidate (Ritalin®), dextroamphetamine (Dexedrine®) or mixed amphetamines (Adderall®) have failed.

With long-term use, abstinence often leads to slow thinking and depression, which in turn requires that the addict use more meth to 'fix' it. A chronic pattern of such behavior is known colloquially as "The Vampire Life."

Serious drug addiction correlates with poor hygiene and general self-care, and even minor health problems can lead to serious complications when left untreated. Striking health problems popularly associated with methamphetamine addiction, such as severe tooth decay or massive skin infections, are caused by unsterilized needles and a lack of hygiene. Even long-term use does not generally result in outward symptoms, but may lead to hypertension, damage to heart valves, and increased risk of strokes.

Routes of administration

The usual route for medical use is oral administration. In recreational use it can be swallowed, snorted, smoked, dissolved in water and injected (or even without water, in what is called a dry shot), inserted anally (with or without dissolution in water), or into the urethra. [23] As with all addictive drugs, the potential for addiction is greater when it is delivered by methods that cause the concentration in the blood to rise quickly, principally because the effects desired by the user are felt more quickly and with a higher intensity than through a moderated delivery mechanism. In fact, studies have shown that the subjective pleasure of drug use (the reinforcing component of addiction) is proportional to the rate that

the blood level of the drug increases. In general, smoking is the fastest mechanism (i.e., it causes the blood concentration to rise the most quickly in the shortest period of time as it allows the substance to travel to the brain through a more direct route than intravenous injection), followed by injecting, snorting, anal insertion, and swallowing.

"Smoking" methamphetamine actually refers to vaporizing it to produce fumes, rather than burning and inhaling the resulting smoke, as with tobacco. It is commonly smoked in glass pipes, or in aluminum foil heated by a flame underneath. This method is also known as "chasing the white dragon" (as derived from the method of smoking opium known as "chasing the dragon"). There is little evidence that methamphetamine inhalation results in greater toxicity than any other route of administration. Lung damage has been reported with long-term use, but manifests in forms independent of route (pulmonary hypertension and associated complications), or limited to injection users (pulmonary emboli).

Injection is a popular method for use, but potentially carries quite serious risks. The hydrochloride salt of methamphetamine is soluble in water; injection users may use any dose from 125 mg to over a gram in one I.V. dose using a small needle. This dosage range may be fatal to non-addicts; addicts rapidly develop tolerance to the drug. Injection users often experience skin rashes (sometimes called "speed bumps") and infections at the site of injection. As with any injected drug, if a group of users shares a common needle or any type of injecting equipment without sterilization procedures, blood-borne diseases such as HIV or hepatitis can be transmitted as well.

Very little research has focused on anal insertion as a method, and anecdotal evidence of its effects is infrequently discussed, possibly due to social taboos in many cultures regarding the anus. This is often known within communities that use meth for sexual stimulation as a "booty bump" or "Keistering," and is anecdotally reported to increase sexual pleasure while the effects of the drug last.[24] The rectum is where the majority of the drug would likely be taken up, through the mucous membranes lining its walls.

Legality

See pseudoephedrine, for legal restrictions placed on that drug as a result of its use as a precursor in the clandestine manufacture of methamphetamine.

Australia

The medical use of methamphetamine is not recognised in Australia and as such it is outlawed.

Canada

Methamphetamine is not approved for medical use in Canada. As of 2005, it falls under Schedule I of the Controlled Drugs and Substances Act. The maximum penalty for the production and distribution is imprisonment for life.

New Zealand

Methamphetamine is a Class A controlled drug under the New Zealand Misuse of Drugs Act 1975. The maximum penalty for production and distribution is imprisonment for life. The maximum penalty for possession is imprisonment for six months. The NZ Misuse of Drugs Act 1975 also covers a "presumption amount". This refers to the quantity of drug that is in a person's possession. If a person is caught with more than a certain amount, it is assumed that the person is in possession of that drug for the purpose of supplying it.

South Africa

In South Africa, methamphetamine is classified as a Schedule 5 drug, and is listed as Undesirable Dependence-Producing Substances in Part III of Schedule 2 of the Drugs and Drug Trafficking Act, 1992 (Act No 140 of 1992).[25] Commonly called "tik", it is mostly abused by youths under the age of 20 in the Cape Flats areas.

United Kingdom

In the UK, methamphetamine was classified as a Class B drug under the Misuse of Drugs Act 1971. The maximum penalty for possession is five years imprisonment, and the maximum penalty for supplying is 14 years. If methamphetamine (or any other Class B drug) is prepared for injection, then it is re-classified as a Class A drug. The maximum penalty for such possession is seven years imprisonment, and the maximum penalty for supplying is life imprisonment.

In 2006, it was announced that methamphetamine is to be reclassified as a Class A drug and has been reclassed as such, following a recommendation made by the Advisory Council on the Misuse of Drugs.[26]

United States

Methamphetamine is classified as a Schedule II substance by the Drug Enforcement Administration under the Convention on Psychotropic Substances.[27] While there is technically no difference between the laws regarding methamphetamine and other controlled stimulants, most medical professionals are averse to prescribing it due to its notoriety.

Methamphetamine is legally marketed in the United States under the trade name Desoxyn, manufactured by Ovation Pharma. Generic formulations of the drug are also available.

Methamphetamine has become a major focus of the 'war on drugs' in the US in recent years. In some areas of the United States, manufacturing methamphetamine is punishable by a mandatory ten-year prison sentence. In certain instances, however, judges have ruled for life in prison without the possibility of parole, especially in cases where victims were killed

by overdoses or impure substances. Crackdowns on the theft of anhydrous ammonia, a substance used in the manufacture of the drug, have resulted in additional prison time.

See also

- Amphetamine
- Phenethylamines

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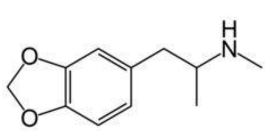
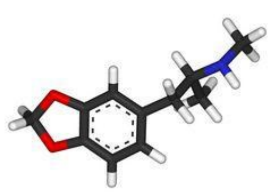
Methylenedioxymethamphetamine

MDMA

1-(benzo[d][1,3]dioxol-5-yl)-N-methylpropan-2-amine

CAS number

42542-10-9
66142-89-0
69610-10-2
81262-70-6

Chemical formula

$C_{11}H_{15}NO_2$

Molecular weight

193.25 g/mol

SMILES

CC(NC)CC1=CC=C(OCO2)C2=C1

Elimination half life

The half-life of MDMA is dose dependent, increasing with higher doses, but is around 6-10 hours at doses of 40-125 mg

Legal status

Schedule I (USA)
Class A (UK)
Schedule III (Canada)

Delivery

75-120 mg tablets
100 mg sublingual

Recreational uses:

euphoria *Other putative uses:* Marriage counseling
Anxiety
PTSD
End of Life Care *Contraindications:* Not for use in combination with stimulants (amphetamines, large doses of caffeine, etc).

Not for use in combination with diuretics (alcohol).

Not for use in individuals with high blood pressure, hypertension, or blood clotting disorders.

Not for use in individuals who have displayed allergies to amphetamine drugs.

Must never be used in combination with MAOI (Monoamine Oxidase Inhibitor) drugs.

Side effects:

Endocrine: hyponatremia *Eye:* dilated pupils

nystagmus *Psychological:* euphoria
strong sense of empathy
serotonin deficiency *Skin:*

- sweaty palms
- heavy sweating
- increased heart rate
- Increased body temperature

Miscellaneous:

- restlessness
- chattering teeth
- muscle spasms

MDMA (*3,4-methylenedioxy-N-methylamphetamine*), most commonly known by the street names *Ecstasy*, *E* or *X*, is a semisynthetic entactogen of the phenethylamine family, whose primary effect is believed to be the stimulation of secretion as well as inhibition of re-uptake of large amounts of serotonin as well as dopamine and norepinephrine in the brain, inducing a general sense of openness, empathy, energy, euphoria, and well-being. Tactile sensations are enhanced for some users, making general physical contact with others more pleasurable; but, contrary to popular belief it generally does not have aphrodisiac effects. Its reported ability to facilitate self-examination with reduced fear may prove useful in some therapeutic settings, leading in 2001 to permission from the United States FDA for testing in patients with post-traumatic stress disorder in conjunction with psychotherapy.

Acute dehydration is a risk among users who are highly physically active and forget to drink water, as the drug may mask one's normal sense of exhaustion and thirst. Also the opposite, "water intoxication," resulting in acute hyponatremia, has been reported as a consequence of use. Sometimes dangerous chemicals such as PMA or methamphetamine alone or in combination with MDMA are added to ecstasy tablets. Long-term effects in humans are largely unknown and the subject of much controversy - particularly with regard to the risks of severe long-term depression as a result of a reduction in the natural production of serotonin.

History

A patent for MDMA was originally filed on Christmas Eve 1912 by the German pharmaceutical company Merck, after being first synthesised for them by German chemist

Anton Köllisch at Darmstadt earlier that year [1][2]. The patent was granted two years later, though in 1916, after two more additional years Köllisch died with no idea of the impact his synthesis would have. At the time, MDMA was not known to be a drug in its own right; rather, it was patented as an intermediate chemical used in the synthesis of a styptic (a drug intended to control bleeding from wounds.) Over half a century would pass before the first recorded ingestion of MDMA by humans.

The U.S. Army did, however, carry out lethal dose studies on MDMA and several other compounds in the mid-1950s. It was given the name *EA-1475*, with the EA standing for Edgewood Arsenal. The results of these studies were not declassified until 1969.

MDMA was legal in the United States until May 31, 1985. Before then, it was used both as an adjunct to psychotherapy and as a recreational drug. MDMA began to be used therapeutically in the mid-1970s after the chemist Alexander Shulgin introduced it to psychotherapist Leo Zeff. As Zeff and others spread word about MDMA, it developed a reputation for enhancing communication, reducing psychological defenses, and increasing capacity for introspection. However, no formal measures of these putative effects were made and blinded or placebo-controlled trials were not conducted. A small number of therapists–including George Greer, Joseph Downing, and Philip Wolfson–used it in their practices until it was made illegal.

MDMA appeared sporadically as a street drug in the early 1970s, but it came into prominence in the early 1980s in certain trendy yuppie bars in the Dallas area, then in gay dance clubs. From there use spread to rave clubs, and then to mainstream society. During the 1990s, along with the growing popularity of the rave subculture, MDMA use became increasingly widespread among young adults in universities and later in high schools. It rapidly became one of the four most widely used illegal drugs in the U.S., along with cocaine, heroin and marijuana.

In the late 1980s and early 1990s, ecstasy was widely used in the United Kingdom and other parts of Europe, becoming an integral element of rave culture. It has also been associated with other psychedelic/dancefloor-influenced music scenes, such as Madchester and Acid House.

Recreational use

The primary effects of MDMA include feelings of openness, euphoria, empathy, love, and heightened self-awareness. Its initial adoption by the dance club sub-culture is possibly due to the enhancement of the overall social and musical experience. Taking MDMA or ecstasy is commonly referred to as popping, rolling, pilling, boshing or dropping in the United Kingdom, "pinging" or "peaking" in Australia, "flipping", "getting chewed" and/or "murfing" in Canada. Some term the rushing feeling of the drug as blowing up, coming up, flying, rolling face,or zooming.

MDMA use has increased markedly since the late 1980s, and spread beyond its original sub-cultures to mainstream use. Prices have also fallen since the 1980s. In countries where distribution is more extensive, such as in the Netherlands and other places in Europe, prices can sometimes be as low as €1 per tablet. In countries where distribution is more difficult, such as the US and Australia, prices are accordingly higher at up to US$10-20 and AUD$35-50 respectively per tablet. In the United Kingdom it is common to pay around £2 to £3 for a

tablet on average. Prices are also usually higher when the drug is purchased in a club or at a rave.

Supply and administration

MDMA is usually ingested in pill form, although use of powder or crystal is increasing in popularity (sometimes known as "Mud," "Molly," "Mandy," "M.D." or "Madman"). Pills come in a variety of "brands", usually identified by the icons stamped on the pills. However the brands do not consistently designate the actual active compound within the pill, as it is possible for "copycat" manufacturers to make their own pills which replicate the features of a well-known brand.

Although full and proper characterization of ecstasy pills requires advanced lab techniques such as gas chromatography-mass spectrometry and gas chromatography-infrared spectroscopy, it is also possible to use a less accurate presumptive alkaloid test known as the Marquis reagent. Many organizations sell testing kits containing this reagent. DanceSafe is one such company, and it includes an extensive database of photographs of different pills, along with the results of a laboratory analysis of their contents. EcstasyData.org [3] is a non-profit site that tests the purity of street pills and compiles results. PillReports.com allows users to post reports of pills they've purchased and share the experience, pictures, and testing results. Other users can then post what they think about the pill in question or even rate the report on the pill.

Effects

Pharmacokinetics

MDMA reaches maximal concentrations in the blood between 1.5 and 3 hours after ingestion. It is then slowly metabolized and excreted, with levels decreasing to half their peak concentration over approximately 8 hrs. Metabolites of MDMA that have been identified in humans include 3,4-methylenedioxyamphetamine (MDA), 4-hydroxy-3-methoxy-methamphetamine (HMMA), 4-hydroxy-3-methoxyamphetamine (HMA), 3,4-dihydroxyamphetamine (DHA, also called alpha-methyldopamine), 3,4-methylenedioxyphenylacetone (MDP2P), and N-hydroxy-3,4-methylenedioxyamphetamine (MDOH). The contributions of these metabolites to the psychoactive and toxic effects of MDMA are an area of active research.

MDMA is known to be metabolized via three pathways. One such pathway proceeds via N-demethylation; byproducts of which include several active metabolites, including MDA. The metabolism may be primarily by the cytochrome P450 enzymes CYP2D6 (in humans, but CYP2D1 in mice), and CYP3A4. Complex, nonlinear pharmacokinetics arise via autoinhibition of CYP2D6 and CYP2D8, resulting in zeroth order kinetics at higher doses. It is thought that this can result in sustained and higher drug concentrations if the user takes consecutive doses of the drug. 65% of MDMA is excreted unchanged in the urine (additionally 7% is metabolised into MDA) during 24 hours after usage

MDMA is a chiral compound and has been almost exclusively administered as a racemate. However, an early uncontrolled report suggests that the S-enantiomer is significantly more potent in humans than the R-enantiomer (Anderson et al. 1978). Studies in humans indicate that the disposition of MDMA is stereoselective, with the S-enantiomer having a shorter elimination half-life and greater excretion than the R-enantiomer. For example, Fallon et al. (1999) reported that the area under the plasma concentration versus time curve (AUC) was two to four times higher for the R-enantiomer than the S-enantiomer after a 40 mg oral dose in human volunteers. Similarly, the plasma half-life of (R)-MDMA was significantly longer than that of the S-enantiomer ((5.8 ± 2.2 hours) vs 3.6 ± 0.9 hours). However, because MDMA has dose dependent kinetics, it is likely that these half lives would be higher at more typical doses (100 mg is sometimes considered a typical dose). Given as the racemate, MDMA has a half-life of around 8 hours.

Short-term neurochemical effects

Serotonin is a neurotransmitter believed to play a role in the regulation of mood and pleasure. MDMA causes serotonin vesicles in the neurons to release quantities of serotonin into the synapses. Although popular press accounts focus on the role of serotonin release, the mechanism by which MDMA causes its unusual psychoactivity is largely unknown. In vitro and nonhuman animal studies have established that MDMA also induces dopamine, norepinephrine, and acetylcholine release and can act directly on a number of receptors, including a2-adrenergic (adrenaline) and 5HT2A (serotonin) receptors. MDMA promotes the release of several hormones including prolactin and the antidiuretic hormone vasopressin, which may be important in its occasional production of water intoxication or hyponatremia.

Subjective effects

Effects desired by users include:

- increased positive emotion and decreased negative emotion
- increased sense of well-being
- increased sociability and feelings of closeness or connection with other people
- reduced defensiveness and fear of emotional injury
- a sense of increased insightfulness and introspective ability

MDMA, particularly with larger doses, is sometimes reported to cause visual distortions. In a review of studies in which 1.5 to 1.7 mg/kg oral MDMA was administered in their laboratory to 74 people, Vollenweider et al. reported that scenic hallucinations were reported only once, while simple patterns, distorted objects, and flashes of light were commonly reported

Other short-term effects

Acute physiological effects include:

- Pupil dilation with attendant photosensitivity and color perception
- Nystagmus
- General restlessness
- Loss of appetite
- Increased heart rate and blood pressure
- Loss of sleep
- Dehydration

Acute toxic/dangerous effects

Apart from the dangers from impurities, the primary acute risks of taking MDMA resemble those of other stimulant amphetamines. The majority of fatalities and cases

requiring emergency care involve hyperthermic syndromes. MDMA appears to decrease heat loss in the body by causing constriction of blood vessels near the skin. In addition, it may sometimes increase heat production by muscles and the brain. These effects may be amplified in people who become dehydrated and are unable to cool by sweating. MDMA can mask the body's normal thirst and exhaustion responses, particularly if a user is dancing or is otherwise physically active for long periods of time without hydration. Because of these effects, MDMA can temporarily reduce the body's ability to regulate its core temperature, and in high-temperature surroundings (e.g. clubs) combined with physical exertion this may lead to hyperpyrexia if precautions are not taken to remain cool. Sustained hyperpyrexia may lead to rhabdomyolysis (muscle breakdown), which in turn can cause renal failure and death.

It has been argued that "the seriousness of the effects can be dependent on environmental factors other than the drug concentration," as blood concentrations of the drug spanned a large range in cases of death in MDMA users. This notwithstanding, "most of the cases of serious toxicity or fatality have involved blood levels... up to 40 times higher than the usual recreational range." (Kalant H., 2001)

While dehydration is undesirable, there also have been a number of users suffering from water intoxication and associated hyponatremia (dilution of the blood that can cause swelling of the brain). Although many cases of this clearly involved individuals drinking large amounts of water, there are cases where there is no evidence of excessive water consumption. Their cases may be caused by MDMA inducing release of the antiduretic hormone vasopressin by the pituitary gland. This causes one to retain water to a greater extent. The death of British teen Leah Betts may be the most widely publicised MDMA-related fatality, and resulted from her consuming too much water due to concerns over dehydration. Signs of hyponatremia include confusion, nausea, headache and loss of consciousness. Hyponatremia in MDMA users is a medical emergency and requires prompt treatment. In general, females are at greater risk of developing symptoms and dying from hyponatremia than males.

MDMA users have also been recorded to demonstrate bruxism (teeth grinding) and trisma (jaw clenching) as a short-term effect from the drug [13] Many users of MDMA alleviate this by using chewing gum [14], however this can result in temporary mouth ulcers through inadvertent biting of the mouth lining. Temporary jaw ache often results from jaw clenching or excessive chewing. Some users consume supplemental magnesium tablets to relax the jaw muscles and relieve clenching.

While users sometimes report increased sexual desire, there are many reports of difficulty achieving orgasm and erection while on the drug. "[MDMA] is a love drug but not a sex drug for most people." (Beck & Rosenbaum, 1994). This is the rationale behind the use of sextasy (combining MDMA with Viagra).

There are reported allergic reactions, which are extremely rare. Liver damage, which may have an immunological cause, has been seen in a small number of users. Animal studies suggest risk and extent of liver damage is increased by high body temperature.

A UK parliamentary committee commissioned report found the use of "Ecstasy" to be less dangerous than tobacco and alcohol in social harms, physical harm and addiction [4]

While most MDMA is taken orally, some users resort to drug injection to achieve a faster, more intense effect. This entails the risks associated with injection of many illicit drugs,

including the transmission of blood-borne viruses, bacterial infections, vein damage and increased chance of overdose.

Addiction and Tolerance

The potential of MDMA to produce addiction (dependence) is controversial. Some studies indicate that many users may be addicted. For example, Cottler et al (2001) interviewed 52 users and found that 43% met standard criteria for dependence. However, some of these people may have been inappropriately diagnosed with dependence because they reported tolerance or after effects from MDMA. Tolerance and after effects ('withdrawal' effects) are symptoms of dependence for many drugs, but seem to occur in some MDMA users who are actually not dependent. For example, studies in Switzerland in which MDMA was given to people who had never used it before documented after effects. When people are classified as addicted to MDMA, it is not clear if that indicates a difficulty in quitting the drug. In a prospective study in Germany, many who were initially categorized as addicted, spontaneously 'improved' without any treatment for the alleged addiction. Given the complexities in classifying MDMA users as addicted, conclusions about the addictive potential of MDMA are less reliable than nicotine addiction.

Long-term adverse effects

Long-term effects are still unknown and heavily debated among scientists. There are several reports of Hallucinogen Persisting Perception Disorder being induced by MDMA. In some cases, the disorder appears to be permanent. The disorder seems to occur in only a small fraction of a percentage of users, and its mechanism of causation is unknown.

Some experiments indicate that use at very high doses may lead to the Synaptic Terminals of serotonin neurons being damaged. The precise mechanism of this action is unknown, but recent evidence (Jones 2004; Miller 1997; Monks et al. 2004) suggests that the metabolic breakdown of MDMA includes the formation of reactive oxygen species (ROS), chemicals known to cause oxidative cell damage when taken up into the releasing synapse.

This effect has been demonstrated experimentally in the brains of rats, where the serotonin terminals of animals who are given extremely high doses of MDMA over a prolonged period of time (usually ten to one hundred times greater than a typical human dose) become withered and useless, although this isn't certain[5][6]. This hypothesis is supported by the fact that the administration of selective serotonin reuptake inhibitors ("SSRIs", which bind to the serotonin cell's reuptake transporters and thus block ROS from entering the serotonin cells) along with or immediately following MDMA seems to block neuron damage in rats given MDMA.

The mechanism proposed as a large part of this neurotoxicity and its functional consequences appear to involve the induction of oxidative stress. This stress results from an increase in free radicals and a decrease in antioxidants in the brain. (Shankaran, 2001) Oxidation is part of the normal metabolic processes of the body. As the cell goes about its life, by-products called oxidative radicals are formed, also called free radicals. These molecules have an unpaired electron that makes them highly reactive. They pull strongly on the

electrons of neighboring molecules and destabilize the electrical balance of those molecules, sometimes causing those molecules to fall apart. This can become a chain reaction.

In normal functioning, there are antioxidants in the system that act as free radical scavengers. These are molecules with an extra electron that they are willing to give up to the free radicals, making both the free radical and the antioxidant more stable. MDMA rapidly increases the levels of free-radicals in the system and overwhelms the reserves of scavengers. The radicals then damage cell walls, reduce the flexibility of blood vessels, destroy enzymes, and cause other molecular damage in the neurological pathways. (Erowid, 2001) It has been shown that MDMA-neurotoxic effects are increased by a hyperthermic environment and decreased by a hypothermic one. (Yeh, 1997)

Studies have suggested that the neurotoxic molecules are not hydroxyl free radicals, but superoxide free radicals. When rats are injected with salicylate, a molecule that scavenges hydroxyl free radicals, the neurotoxic effects of MDMA are not attenuated, but actually potentiated. Further evidence of this superoxide theory comes from the observation that CuZn-superoxide dismutase transgenic mice (mice with excess human antioxidant enzyme) demonstrate neuroprotective mechanisms that protect the mice from MDMA-induced depletion of 5-HT (serotonin) and 5-HIAA and lethal effects. (Baggott, 2001 and Yeh, 1997)

Studies giving animal species injections have shown that ascorbic acid, alpha lipoic acid, l-cysteine, and some other radical scavengers are effective in reducing oxidative stress caused by MDMA. (Erowid, 2001) A combination of antioxidants, including Vitamin A, C, and E are recommended; taking multivitamins including selenium, riboflavin, zinc, cartenoids, etc. should help reduce oxidative damage. Many of these vitamins, though, are water soluble, and are quickly excreted from the body. The typical MDMA user is psychoactive for 4-6 hours and may not have an appetite from the time of taking until the following sleep cycle or many hours later. These vitamins flush through the system in 3-4 hours. Damage occurs in the absence of these antioxidants.

There are some fallacies in applying these animal studies to human use. Firstly, it is difficult to equate rat doses to human doses, rats metabolise MDMA twice as fast as humans and often larger doses or multiple doses are administered to simulate human plasma levels. The doses given in experiments are far greater than typical human use of 100-300 mg in order to notice the problems caused so that we may say that if this happens at large doses, then a lesser form should happen at low doses. There could be a threshold of nothing happening or a threshold of the worst problems at low doses.

Secondly, the effective doses of antioxidants given to these animals are much higher than humans would ever take both in its method of administration (injected vs. oral) and in its dosage. Essentially both the neurotoxic and neuroprotective effects are exaggerated, but it is not possible to say if this scales down the same way.

Some MDMA users administer an SSRI while, or shortly after taking MDMA, in an attempt to prevent possible neurotoxicity. These SSRIs are typically antidepressants such as fluoxetine or

However, MDMA use in conjunction with a different class of antidepressants, namely Monoamine oxidase inhibitors, is strongly contra-indicated due to danger of serotonin syndrome and the possibility of life-threatening hypertension. The safety of this practice has not been systematically evaluated.

Many users also attempt to replenish the deficit of serotonin which follows the use of MDMA [7] by administering 5-HTP, in an attempt to alleviate to a degree the depression and overall mental unsettlement in the days following MDMA usage [8] (including the immediate "come-down" and what is known as "suicide Tuesday"). The serotonin precursor 5-HTP, which is commercially available as a dietary supplement, reportedly supplies the user with more of the raw materials to synthesize the neurotransmitter, reducing the negative psychological effects of depleted serotonin. Pre-loading with 5-HTP has not been shown to increase the subjective effects of MDMA. Anecdotal reports seem to indicate this is largely placebo with some users reporting a moderate muting of the MDMA effect when 5-HTP is consumed within 24 hours prior to MDMA use.[9]

Because the neurotoxicity of MDMA is believed by some to be highly dependent on its metabolic disposition (Jones 2004; de la Torre & Farré 2004), it is unclear how to generalize to humans from experiments in rats and monkeys.

Considerable research has been done into possible cognitive-behavioral deficits among ecstasy users but data have been largely inconclusive. At least two meta-analyses of these studies have been completed (Morgan 2000; Sumnall & Cole 2005). Morgan's analysis of 17 studies showed that ecstasy users had a slight tendency to be more impulsive and depressed than controls. Sumnall and Cole's analysis showed a slight increase in the prevalence of depressive symptoms in ecstasy users over controls. Of course, in retrospective studies like these we are always faced with a chicken-or-egg question: did these impulsive and depressed people use ecstasy to self-medicate or did otherwise normal people become depressed and impulsive after using ecstasy? This question has not been answered.

Although some experimental evidence exists indicating that long-term ecstasy users experience memory difficulties, a large study in 2002 (Strote et al.) showed that ecstasy users in 4-year colleges have GPAs which do not differ significantly from those of non-users.

MDMA and Parkinson's

Research at the University of Manchester indicates that MDMA dramatically reduces tremors in patients receiving L-DOPA treatment for Parkinson's disease.

In a now-retracted study, a research team led by Dr. George A. Ricaurte at Johns Hopkins University implicated MDMA as a cause of Parkinson's-like brain abnormalities in monkeys, suggesting that a single use of MDMA caused permanent and serious brain damage. These claims were hotly disputed by physicians, therapists, and other experts in the field, including a team of scientists at New York University. Criticisms of the study included its use of injection rather than oral administration; that this type and scale of damage (>20% mortality) would translate to hundreds of thousands or millions of deaths which had not materialized in the real world amidst extremely broad global MDMA usage; and, perhaps most important, that other research teams could not duplicate the study's findings.

On September 6, 2003, Dr. George A. Ricaurte and his team announced that they were retracting all results of their commonly cited and controversial study. The researchers said that the labels on the drugs had been somehow switched, and they had inadvertently injected their experimental monkeys and baboons with extremely high doses of methamphetamine instead of MDMA. The chemical supplier, Research Triangle Institute, has publicly claimed

that the proper drug was supplied, and Ricaurte has yet to pursue them for their alleged error.

Ricaurte had also come under fire for supplying PET scans to the U.S. Office of National Drug Control Policy that were used in anti-drug literature (Plain Brain/Brain After Ecstasy) that seemed to suggest MDMA created holes in human brains, an implication that critics called misleading. Ricaurte later asked the Agency to change the literature, citing the "poor quality" of the images. These images are still circulating in educational systems across the U.S., however, and the myth that ecstasy users develop "holes in their brains" remains quite popular and government funded.

Legal issues

Use, supply and trafficking of ecstasy are currently illegal in most countries. In the United States, MDMA was legal and unregulated until May 31st 1985, at which time it was added to DEA Schedule I, for drugs deemed to have no medical uses and a high potential for abuse. During DEA hearings to criminalize MDMA, most experts recommended DEA Schedule III prescription status for the drug, due to its beneficial usage in psychotherapy. The judge overseeing the hearings, Francis Young, also made this recommendation. Nonetheless, the DEA classified it as Schedule I[10].

That same year, the World Health Organization's Expert Committee on Drug Dependence recommended that MDMA be placed in Schedule I of the Convention on Psychotropic Substances. Unlike the Controlled Substances Act, the Convention has a provision (in Article 7(a)) that allows use of Schedule I drugs for "scientific and very limited medical purposes". The Committee's report stated

> The Expert Committee held extensive discussions concerning therapeutic usefulness of 3,4 Methylenedioxymethamphetamine. While the Expert Committee found the reports intriguing, it felt that the studies lacked the appropriate methodological design necessary to ascertain the reliability of the observations. There was, however, sufficient interest expressed to recommend that investigations be encouraged to follow up these preliminary findings. To that end, the Expert Committee urged countries to use the provisions of article 7 of the Convention on Psychotropic Substances to facilitate research on this interesting substance.

In the United Kingdom, MDMA is a Class A drug under the Misuse of Drugs Act 1971, making it illegal to sell, buy, or possess without a license. Penalties include a maximum of seven years and/or unlimited fine for possession; life and/or unlimited fine for production or trafficking. A mandatory seven year sentence is now the penalty for a third conviction for trafficking.

Medical use and clinical studies

In 2001, the FDA granted permission for experimental administration of MDMA to patients suffering from post-traumatic stress disorder. This research is being sponsored by the Multidisciplinary Association for Psychedelic Studies (MAPS). For further information on this, see MAPS's MDMA Research Information and the recent article from MSNBC/Newsweek. This research in patients builds on studies in which MDMA was given to

healthy volunteers. The first of these healthy volunteer studies was conducted by Dr. Charles Grob, with other studies done by Dr. Franz Vollenweider in Switzerland, Drs. John Mendelson and Reese Jones at the University of California San Francisco, and Drs. Magi Faree and Rafael de la Torre in Spain.

Safety and contraindications

The illegality of this drug in many countries makes exact study of its effects difficult. Some safety considerations to consider with the use of ecstasy, which may or may not be conclusive, are the following:

- Because of its illegality, the dose and purity of an ecstasy pill varies dramatically. The dose may be stronger than is advertised, may be adulterated, or might not even contain MDMA.
- Ecstasy affects the regulation of the body's internal systems. Continuous dancing without sufficient breaks or drinks can lead to dangerous overheating and dehydration. Drinking too much water without consuming a corresponding amount of salt can lead to hyponatremia or Water intoxication.
- The use of ecstasy can exacerbate depression and may produce temporary depression as an after-effect for some users. Some individuals also might experience wild or unexpected mood swings the first couple of days following the use of MDMA.
- The use of ecstasy can be very dangerous when combined with other drugs (particularly monoamine oxidase inhibitors (MAOIs) and antiretroviral drugs, in particular Ritonavir). Combining MDMA with MAOIs can precipitate a hypertensive crisis and can result in a near-fatal repercussion.
- In some cases, pills marketed as ecstasy do not contain only MDMA, but instead are substituted with various substances like ketamine, methamphetamine and caffeine. Some users purchase testing kits to verify that pills are actually MDMA. Organizations such as DanceSafe provide testing kits. One effect of this in Europe, and particularly the UK, has been to make pure MDMA powder (known as "Dabs") and crystals (known as "Crystal", not to be confused with Methamphetamine, which is known as Crystal in the US) increasingly popular. In some areas of the UK, pure forms of MDMA are easier to get hold of than Ecstacy pills.
- Long-term after-effects are greatly exacerbated by high doses and frequent use.
- A small percentage of users may be highly sensitive to MDMA; this may make first-time use especially hazardous. This includes but is not limited to people with congenital heart defects. Some scientists have suggested that a small percentage of people lack the proper enzymes to break down the drug. One enzyme involved in MDMA's breakdown is CYP2D6, which is deficient or totally absent in 5-10% of the caucasian population and those of African descent and 1-2% of Asians. However, there is no clear evidence linking lack of this enzyme to problems in users and the connection remains theoretical.

See also

- Empathogen-entactogen
    - Amphetamine
- Phenethylamines
- Psychoactive drug
-

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Selective serotonin reuptake inhibitor

Selective serotonin reuptake inhibitors (*SSRIs*) are a class of antidepressants used in the treatment of depression, anxiety disorders and some personality disorders. Studies have also found that SSRIs, as a side effect of their action, may cause in many people either a delay of sexual climax or anorgasmia, so they can be used to develop drugs specifically targeted to treat premature ejaculation.

SSRI drugs are designed to allow the available neurotransmitter serotonin to be utilized more efficiently. A low level of utilization of serotonin is currently seen as one among several neurochemical symptoms of depression. Low levels of serotonin in turn can be caused by an anxiety disorder, because serotonin is needed to metabolize stress hormones .

These medications evolve their effects at the serotonin transporter. They increase the extracellular level of the neurotransmitter serotonin by inhibiting its reuptake into the presynaptic cell. They have no or only weak effects on other monoamine transporters, thus having little direct influence on the level of other neurotransmitters. That distinguishes them from the older tricyclic antidepressants (TCAs), thus they are named selective. SSRIs are considered to be considerably safer than TCAs, since the toxic dose is much higher and they are said to have fewer and weaker side effects and drug interactions.

List of SSRIs

Many drugs in this class are familiar in the USA through advertising, including the following:
(Trade names in parentheses)

- citalopram (Celexa, Cipramil, Emocal, Sepram, Seropram)
escitalopram oxalate (Lexapro, Cipralex, Esertia)
fluoxetine (Prozac, Fontex, Seromex, Seronil, Sarafem, Fluctin (EUR))
fluvoxamine maleate (Luvox, Faverin)
- Paroxetine (Paxil, Seroxat, Aropax, Deroxat, Paroxat)
- Zoloft, Lustral, Serlain)
- dapoxetine (no known trade name)

Escitalopram is simply the left-handed s-enantiomer of the racemic citalopram. It had been introduced to the market just before the patent protection for citalopram had expired.

It is commonly thought that that the primary action of St. John's wort is as an SSRI.

Note that trazodone is not a typical member of the SSRIs - while it is a serotonin reuptake inhibitor, it is believed that its anti-depressant properties may be due to some of its other pharmacokinetic properties rather than its effect on serotonin reuptake inhibition. That said, it does still share many properties of the typical SSRIs, especially the possibility of the so-called 'discontinuation syndrome' (see the section on this below).

Medical indications

The main indication for SSRIs is major depression. Apart from this, SSRIs are frequently prescribed for anxiety disorders, panic disorders, obsessive-compulsive disorder (OCD), social phobia and eating disorders. Though not specifically indicated by the manufacturers, they are also sometimes prescribed to treat irritable bowel syndrome (IBS). Additionally, SSRIs have been found to be effective in treating premature ejaculation in up to 60% of men.

Contraindications / drug interaction

SSRIs are contraindicated with concomitant use of MAOIs (monoamine oxidase inhibitors). This can lead to increase serotonin levels which could cause a serotonin

syndrome. People taking SSRIs should also avoid taking pimozide (a diphenylbutylpiperidine derivative). The non-opioid analgesic tramadol hydrochloride (or Ultram, Ultracet) can, in rare cases, produce seizures when taken in conjunction with an SSRI or tricyclic antidepressant.

Mode of action

Basic understanding

In the brain, messages are passed between two nerve cells via a synapse, a small gap between the cells. The cell that sends the information releases neurotransmitters (of which serotonin is one) into that gap. The neurotransmitters are then recognized by receptors on the surface of the recipient (postsynaptic) cell, which upon this stimulation, in turn, relays the signal. About 10% of the neurotransmitters are lost in this process, the other 90% are released from the receptors and taken up again by monoamine transporters into the sending (presynaptic) cell (a process called reuptake).

Some theories link depression to a lack of stimulation of the recipient neuron at a synapse. To stimulate the recipient cell, SSRIs inhibit the reuptake of serotonin. As a result, the serotonin stays in the synaptic gap longer than it normally would, and has the chance to be recognized again (and again) by the receptors of the recipient cell, which can finally be stimulated fully.

Pharmacodynamics

SSRIs inhibit the reuptake of the neurotransmitter serotonin (5-hydroxytryptamine or 5-HT) into the presynaptic cell, increasing levels of 5-HT within the synaptic cleft.

But there is one counteracting effect: high serotonin levels will not only activate the postsynaptic receptors, but also flood presynaptic autoreceptors, that serve as a feedback sensor for the cell. Activation of the autoreceptors (by agonists like serotonin) triggers a throttling of serotonin production. The resulting serotonin deficiency persists for some time, as the transporter inhibition occurs downstream to the cause of the deficiency, and is therefore not able to counterbalance it. The body adapts gradually to this situation by lowering (downregulating) the sensitivity of the autoreceptors.

Of greater importance is another adaptive process: the downregulation of postsynaptic serotonin 5-HT$_{2A}$ receptors.

These (slowly proceeding) neurophysiological adaptions of the brain tissue are the reason why usually several weeks of continuous SSRI use are necessary for the antidepressant effect to become fully manifested.

Interaction with carbohydrate metabolism

Serotonin is also involved in regulation of carbohydrate metabolism. Few analyses of the role of SSRI's in treating depression cover the effects on carbohydrate metabolism from intervening in serotonin handling by the body.

Neuroprotection

Studies have suggested that SSRIs may promote the growth of new neural pathways.[1] Also, SSRIs may protect against neurotoxicity caused by other compounds (for instance MDMA and Fenfluramine) as well as from depression itself.

SSRIs versus TCAs

SSRIs are described as 'selective' because they affect only the reuptake pumps responsible for serotonin, as opposed to earlier antidepressants, which affect other monoamine neurotransmitters as well. Because of this, SSRIs lack some of the side effects of the more general drugs.

There appears to be no significant difference in effectiveness between SSRIs and tricyclic antidepressants, which were the most commonly used class of antidepressants before the development of SSRIs.[2] However, SSRIs have the important advantage that their toxic dose is high, and, therefore, they are much more difficult to use as a means to commit suicide. Further, they were initially claimed to have fewer and milder side effects.

SSRIs versus 5-HT-Prodrugs

Serotonin cannot be administered directly because when ingested orally, it will not cross the blood-brain barrier, and therefore won't have an effect on brain functions. Also, serotonin would activate every synapse it reaches, whereas SSRIs only enhance a signal that is already present, but too weak to come through.

Biosynthetically serotonin is made from tryptophan, an amino acid. If depression is caused by lack of serotonin, rather than insensitivity to it, SSRIs alone will not work well, whereas supplementing with tryptophan will. In 1989, the Food and Drug Administration made tryptophan available by prescription only, in response to an outbreak of eosinophilia-myalgia syndrome caused by impure L-tryptophan supplements sold over-the-counter. With current standards, L-tryptophan is again available over the counter in the US as well as supplement 5-HTP which is a direct precursor to serotonin.

Adverse effects

General side effects

General side effects are mostly present during the first 1-4 weeks while the body adapts to the drug. Almost all SSRIs are known to cause either one or more of these symptoms:

- nausea
- drowsiness
- headache
- changes in weight and appetite
- changes in sexual behaviour (see the next section)

- increased feelings of depression and anxiety
- tremors
- increased sweating

It is not recommended to quit the medication because of the side effects, as they usually disappear after the adaptation phase and at the same time the antidepressive effects begin to show. However, despite being called general, the side effects and their duration is highly individual and drug-specific, so usually the treatment is begun with a small dose to see how the patient's body reacts to the drug. After that either the dose can be increased or the drug can be changed to some other if the side effects won't disappear or the patient feels they are too uncomfortable.

Suicidality

Over the years there have been many accusations by patients and their families of SSRIs causing suicidal ideation and behavior, but as there is little scientific support for this claim, judicial evidence is piling up that patients committed suicide after using SSRIs.[3] Manufactures of SSRIs historically have vehemently denied any such link and have always blamed the disease rather than the treatment. In 2003 the UKs Committee on Safety of Medicines banned [4] the use of paroxetine (known in that country as Seroxat) in the use of children due to evidence of increased harm and potentially suicidal behaviour. In early 2006 GlaxoSmithKline issued a press release[5] stating that new meta-analysis of their clinical trial data has revealed a statistically significant higher frequency of suicidality in patients treated with their SSRI, paroxetine (Paxil) than with placebo.

In the United States there is a required box warning for suicide risk in children but not for adults.

Sexual side effects

It is well known that the selective serotonin reuptake inhibitors (SSRIs) can cause various types of sexual dysfunction such as anorgasmia, erectile dysfunction, and diminished libido. Initial studies found that such side effects occur in less than 10% of patients, but those studies relied on unprompted reporting, so the frequency of such problems was underestimated. In more recent studies, doctors have specifically asked about sexual difficulties, and found that they are present in between 41%[6] and 83% of patients.[7] This dysfunction occasionally disappears spontaneously without stopping the SSRI, and in most cases resolves after discontinuance. In some cases, however, it does not; this is known as PSSD.

It is believed that sexual dysfunction is caused by an SSRI induced reduction in dopamine. Stimulation of postsynaptic 5-ht2 and 5-ht3 receptors decreases dopamine release from the Substantia Nigra. Sexual dysfunction caused by SSRI's can sometimes be mitigated by several different drugs. These include bupropion, buspirone, methylphenidate, mirtazapine, Amphetamine, pramipexole and ropinirole.

Because of these sexual side effects, the SSRI fluoxetine (Prozac) was recently classified as a reproductive and developmental toxin by the Center for the Evaluation of Risks to Human Reproduction (CERHR), an expert panel at the National Institute of Environmental Health Sciences at the National Institutes of Health.

PANES

Persistent Adverse Neurological Effects following SSRI discontinuation (PANES) are serious side-effects induced by an SSRI that remain or worsen after both the medicine has been completely eliminated from the body, and after SSRI discontinuation syndrome (if it occurs) ends.

Overdose

SSRIs appear to be safer in overdose when compared with traditional antidepressants such as the tricyclic antidepressants. This relative safety is supported both by case series and studies of deaths per numbers of prescriptions.[8] However, case reports of SSRI poisoning have indicated that severe toxicity can occur[9] and deaths have been reported following massive single ingestions,[10] although this is exceedingly uncommon when compared to the tricyclic antidepressants.[8]

Because of the wide therapeutic index of the SSRIs, most patients will have mild or no symptoms following moderate overdoses. The most commonly reported severe effect following SSRI overdose is serotonin syndrome; serotonin toxicity is usually associated with very high overdoses or multiple drug ingestion.[11] Other reported significant effects include coma, seizures, and cardiac toxicity.[8]

Treatment for SSRI overdose is mainly based on symptomatic and supportive care. Medical care may be required for agitation, maintenance of the airways, and treatment for serotonin syndrome. ECG monitoring is usually indicated to detect any cardiac abnormalities.

Criticism of SSRIs

SSRIs have been the focus of controversy. Some feel that SSRIs are prescribed by overzealous doctors or psychiatrists in cases where their use is only marginally indicated. In late 2004 much media attention was given to a proposed link between SSRI use and juvenile suicide. For this reason, the use of SSRIs in pediatric cases of depression is now recognized by the FDA as warranting a cautionary statement to the parents of children who may be prescribed SSRIs by a family doctor. The FDA's currently required packaging insert for SSRIs includes a warning (known as a "black box warning") that a pooled analysis of placebo controlled trials of 9 antidepressant drugs (including multiple SSRIs) resulted in a risk of suicidality that was twice that of placebo. Other studies have shown no increase in rates of suicide but a small increase of non-fatal self-harm[12] and even of reduced incidence of suicide.[13] [14][15]

Critics have also alleged that the widely disseminated television and print advertising of SSRI drugs promotes an inaccurate message, oversimplifying what these medications actually do and perhaps misinforming the public, contributing to the problems listed above.[16] Much of the criticism stems from questions about the validity of claims that such drugs work by correcting chemical imbalances.

Other medications to treat depression

The majority of medications most recently approved to treat depression work on multiple neurotransmitters. Venlafaxine and duloxetine (Cymbalta) are both members of the SNRI class of antidepressant medication. SNRIs (serotonin-norepinephrine reuptake inhibitors) work on the norepinephrine and serotonin neurotransmitters. Mirtazapine also increases levels of norepinephrine and serotonin, but it is a tetracyclic antidepressant, not a

SSRI or SNRI. The arrival of these new drugs suggest that future antidepressants will not work on serotonin exclusively. Since the expiration of Eli Lilly's Prozac patent, Lilly has been promoting their new SNRI, duloxetine. Natural healing professionals often recommend 5-HTP supplements instead of standard SSRI/MAOI prescriptions as 5-HTP allegedly accomplishes the same goal without resorting to disturbing the brain's natural metabolic procedures, although this has not been scientifically proven.

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Paroxetine

Systematic (IUPAC) name

(3S-trans)-3-((1,3-Benzodioxol-5-yloxy)methyl)- 4-(4-fluorophenyl)-piperidine

Identifiers

CAS number rn=1" href="http://www.nlm.nih.gov/cgi/mesh/2006/MB_cgi?term=61869-08-7&rn=1"> 61869-08-7

ATC code N06**AB05**

PubChem 43815

DrugBank APRD00364

Chemical data

Formula $C_{19}H_{20}NFO_3$

Mol. weight 374.8

Pharmacokinetic data

Bioavailability complete absorption from GI, but extensive first-pass-metabolization in the liver; max concentration 4.9 (with meals) to 6.4 hours (fasting)

Metabolism extensive, probable hepatic

Half life 24 hours (range 3-65 hours)

Excretion 66% urine, 37% bile

Therapeutic considerations

Licence data US

Pregnancy cat. D(US)

Legal status P*rescription only*

Routes Oral

Paroxetine or *paroxetine hydrochloride* is a selective serotonin reuptake inhibitor (SSRI) antidepressant. It was released in 1992 by the pharmaceutical company GlaxoSmithKline and has since become one of the most prescribed antidepressants on the market due to its efficacy in treating depression as well as a spectrum of anxiety disorders ranging from panic attacks to phobias.

Trade names

Paroxetine is marketed under several tradenames:

- *Aropax* or *Oxetine* in Australia, New Zealand, South Africa, Argentina and Brazil
- Aroxat *or* Aroxat CR *in Chile*
- *Cebrilin* in Latin America
- *Deroxat* in Switzerland and France
- *Optipar* in Finland
- *Paroxat* in Germany and Hungary
- *Paxil or Paxil CR* in the United States, Canada, Argentina and Brazil
- *Pondera* in Brazil
- *Seroxat* in Austria, Belgium, Finland, Greece, Israel, The Netherlands, Poland, Portugal, Singapore, Spain, Turkey, the UK and China.

Indications

Approved

Paroxetine is primarily used to treat the symptoms of depression, obsessive-compulsive disorder (OCD), post-traumatic stress disorder (PTSD), panic disorder, generalized anxiety disorder (GAD), [1] social phobia/social anxiety disorder, [2] and premenstrual dysphoric disorder (PMDD).[3]

It was the first (and as of 2002, the only) antidepressant formally approved in the United States for the treatment of social anxiety disorder, causing it to be sometimes referred to (although inaccurately) as an anti-shyness drug.

Clinical Trials

Trials for Paxil CR have not lasted more than twelve months. The effectiveness of Paxil in major depressive disorders has been proven by two twelve week clinical trials in which the patients either had flexible doses or a placebo. Both of the studies concluded that Paxil is significantly more effective than the placebo control group. For another disorder, three 10-week studies were conducted to prove the effectiveness of Paxil CR on panic disorders. In the first and second studies, Paxil proved consistently better than the placebo. But the third

trial Paxil CR failed to have any significant difference to the placebo. For social anxiety disorder, a 12-week trial for adult outpatients was conducted to show Paxil's effectiveness against the disease and prior information of Paxil's nature in the immediate release formulation. The study did not include adolescents with the disorder.

Unapproved/Off-label/Investigational

Paroxetine can also be used in the treatment of premature ejaculation,[4] chronic headache,[5] and bipolar disorder.[6]

Paroxetine has been found to significantly reduce the symptoms of diabetic neuropathy.[7]

There is also evidence that paroxetine may be effective in the treatment of compulsive gambling[8] and hot flashes.[9]

Pharmacology

Paroxetine is the most potent selective serotonin (5-hydroxytryptamine, 5-HT) reuptake inhibitor (SSRI). This activity of the drug on brain neurons is thought to be responsible for its antidepressant effects.

Paroxetine is a phenylpiperidine derivative which is chemically unrelated to the tricyclic or tetracyclic antidepressants. In receptor binding studies, paroxetine did not exhibit significant affinity for the adrenergic (±1, ±2, ^{2}), dopaminergic, serotonergic (5HT1, 5HT2), or histamine receptors of rat brain membrane. A weak affinity for the muscarinic acetylcholine and noradrenaline receptors was evident. The predominant metabolites of paroxetine are essentially inactive as 5-HT reuptake inhibitors.

Paroxetine controlled release (CR)

Paroxetine controlled release contains a Geomatrix™ tablet that controls the absorption of the drug. Clinical studies show that controlled release tablet provides effective symptom relief with a lower number of patients stopping their treatment due to side effects.[10]

However, the need for an extended release form of paroxetine has not been established, as the FDA indicated that the half-life for the original Paxil was ideal for once-daily dosing, and that a CR version was not needed.

Chemistry

Paroxetine hydrochloride is an odorless, off-white powder, having a melting point range of 120° to 138°C and a solubility of 5.4 mg/mL in water.

Formulations

Paxil / Seroxat (paroxetine) is available in 10, 20, 30, and 40 mg tablets.

Paxil CR (paroxetine extended release) is available in 12.5, 25, and 37.5 mg tablets.

Paxil, Seroxat and Paxil CR are manufactured by GlaxoSmithKline, however a generic is now available under the chemical name paroxetine.

Side effects

General side effects are mostly present during the first 1-4 weeks while the body adapts to the drug. Almost all SSRIs are known to cause either one or more of these symptoms. A person receiving paroxetine treatment may experience a few, all, or none of the following side-effects, and most side-effects will disappear or lessen with continued treatment, though some may last throughout the duration.

- Nausea
Drowsiness
Headache
Changes in weight and appetite
Changes in sexual behaviour
Increased feelings of depression and anxiety (initially)
Dry mouth
Constipation
Diarrhea
Aggressive behavior (esp. in children)
Possible suicidal behavior
Possible congenital malformations
Rash
Restlessness or Akathisia
Itch
Sodium depletion
Changes in urination
Sweating
Muscle weakness
Uncharacteristic levels of aggression
Inability to reach orgasm and other sexual side effects

Individuals experiencing any of the following symptoms should contact their doctor immediately:

- Jaw, neck, and back muscle spasms
Fever, chills, sore throat, or flu-like symptoms
Yellowing of the skin or eyes
Black, tarry stools (this can indicate upper GI bleeding)

Paroxetine and other SSRIs have been shown to cause sexual side effects in some patients, both males and females. Although usually reversible, these sexual side effects can sometimes last for months, years or possibly indefinitely even after the drug has been completely withdrawn. This disorder is known as Post SSRI Sexual Dysfunction.

Discontinuation syndrome

While any psychoactive medication (from caffeine to anti-psychotics) can cause withdrawal symptoms upon discontinuation from acute administration, anecdotal evidence suggests that paroxetine has a higher incidence rate and severity of SSRI discontinuation syndrome than other SSRIs and psychoactive medications. For those experiencing extreme and unusual difficulty discontinuing paroxetine, it is recommended that an SSRI with a

longer half-life, such as fluoxetine, be administered for approximately two weeks, then discontinued, to lessen symptoms.[11][12]

Suicidal ideation is a frequently reported experience in those withdrawing from SSRIs.[13] Withdrawal from paroxetine or any other SSRI should be medically supervised.

Footnotes

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Sertraline (Zoloft)

Systematic (IUPAC) name

(1S)-cis-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-N-methyl-1-naphthalenamine

Identifiers

CAS number rn=1" href="http://www.nlm.nih.gov/cgi/mesh/2006/MB_cgi?term=79617-96-2&rn=1"> 79617-96-2

ATC code N06**AB06**

PubChem 68617

DrugBank APRD00175

Chemical data

Formula $C_{17}H_{17}NCl_2$

Mol. weight 342.7 g/mol

Pharmacokinetic data

Bioavailability **44%**

Metabolism N-demethylation (liver)

Half life ~26 hours

Excretion Renal

Therapeutic considerations

Pregnancy cat. C

***Legal status P**rescription only*

Routes Oral

Sertraline hydrochloride (also labeled under numerous brand names: *Zoloft*, *Sertralin*, *Lustral*, *Apo-Sertral*, *Asentra*, *Gladem*, *Serlift*, *Stimuloton*, *Xydep*, *Serlain*, *Concorz*) is an orally administered antidepressant of the selective serotonin reuptake inhibitor (SSRI) type. It was first approved by the Food and Drug Administration (FDA) in 1991.

Invention

The invention of Sertraline has been attributed to two scientists at Pfizer: Steve Werner and Billy Dzomba. At the time, the notion that the neurotransmitter serotonin and depression might be linked was a fairly new concept. Together, Werner and Dzomba explored a variety of potential anti-depressant compounds and, within the space of one year, developed Sertraline.[1]

Indications

Approved

Sertraline is used medically mainly to treat the symptoms of depression and anxiety. It is also prescribed for the treatment of obsessive-compulsive disorder (OCD),[2] post-traumatic stress disorder (PTSD),[3] premenstrual dysphoric disorder (PMDD),[4] panic disorder (PD)[5] and social phobia/social anxiety disorder.[6]

Unapproved, off-label, and investigational

Sertraline can also be used in the treatment of general anxiety disorder,[7] binge eating disorder,[8] and premature ejaculation.[9]

There is also evidence that sertraline may be effective in the treatment of refractory neurocardiogenic syncope in children and adolescents.[10]

A study has shown that sertraline is an effective treatment for impulsive aggressive behavior in personality disordered patients.[11]

Side effects

Sertraline can have adverse effects, including: Sleep disorder (both insomnia and increased sleep time), asthenia, gastrointestinal complaints, tremors, confusion, dizziness, anorgasmia, nauseua/vomiting, and decreased libido; it can induce mania or hypomania in around 0.5% of patients. It has also been known to cause minor weight loss. It is contraindicated in individuals taking monoamine oxidase inhibitors (MAOIs) or undergoing electroconvulsive therapy. It is advised you are off MAOI for at least 14 days before beginning to consume Zoloft. (http://drugs.com/zoloft.html)

Until 2003, Zoloft was only approved for use in adults ages 18 and over; that year it was approved by the FDA for use in treating children ages 6 to 17 with extreme obsessive compulsive disorder. In June 2004, Britain banned Zoloft's use by minors and in February 2005, Pfizer was forced to change Zoloft's labeling to include information regarding increased incidences of suicidal behavior and depression in adolescent users of the drug. According to mentalhealth.com, Zoloft is not currently recommended or advised for use in individuals under the age of 18. After these changes, multiple incidences and at least one medical study showed an increased suicide risk in seniors who were taking Zoloft. In response to these findings, the FDA released a public health warning. This warning indicates that anyone currently using Zoloft for any reason has a greater chance of exhibiting suicidal thoughts or behaviors regardless of age. This warning is questionable, however, due to the types of illnesses Zoloft is used to treat, it is impossible to determine if these tendencies are a side effect of the drug or the illness the drug is meant to treat. Zoloft should still truly be only recommended in rather persistent cases as drugs such as these are still in the arena of the unknown.

Zoloft has long been seen as the best option for breastfeeding mothers who wish to continue breastfeeding and be able to take their antidepressants. Despite its apparent safety and effectiveness during the breastfeeding period, recent studies and consumer complaints have seen a need to alter Zoloft's labeling regarding use during the third trimester of pregnancy. Though there are no teratogenic effects associated with Zoloft, there is reason to be concerned about its effects on infants who were exposed to sertraline during the third trimester in utero. It seems that Zoloft use in late pregnancy significantly increases the potential need for hospitalization and breathing assistance in the newborn period and has also been shown to cause an increased risk of neonatal death. In light of this increased risk it is still being used due to the greater potential risk of a seriously depressed mother to herself and her fetus. Like all other medications Zoloft's use must be decided only after carefully weighing out all potential risks and benefits.

Although SSRI anti-depressants may cause problems in newborn babies whose mothers took Zoloft during pregnancy, the ceasing of Zoloft consumption during pregnancy may cause a relapse of depression. If you are planning on becoming pregnant, or are currently pregnant and are taking Zoloft, do not stop taking this medication. Consult your physician first. (http://www.drugs.com/zoloft.html)

According to the manufacturer's website, "if depression is left untreated, the risk of childhood suicide increases about 12 times, according to federal figures". (http://www.zoloft.com)

Sertraline and other SSRIs have been shown to cause sexual side effects in 40-75% of both males and females taking them. This disorder is known as Post SSRI Sexual Dysfunction.

Distribution

This drug has been heavily prescribed in the United States. According to one source, more than 115 million prescriptions for Sertraline had been written in the U.S. by February of 2000.[12] The world over, $3.5 billion worth of Zoloft was sold in 2005.[13]

Formulations

Sertraline is manufactured by Pfizer and sold as Zoloft in the United States as small green 25 mg tablets, blue 50 mg tablets, and yellow 100 mg tablets (Generic 100 mg sertraline tablets are also yellow), each of which is scored to allow easy halving.

In the UK, the brand name is Lustral and is available in white 50 mg or 100 mg scored tablets, according to the British National Formulary (BNF). Elsewhere in the EU the brand name is Zoloft, available in white 50 mg or 100 mg scored tablets. In Australia, only the 50 mg and 100 mg strengths are available, both as white tablets.

Sertraline is an odorless, white, sparingly soluble crystalline solid. The minimum effective dose is usually 50 mg per day (it can be still effective at 25 mg or 37.5 mg), but lower doses may be used in the initial weeks of treatment to acclimate the patient's body, especially the liver, to the drug and to minimize the severity of any side effects. Patients who do not experience relief of symptoms at 50 mg a day may have their dose increased, up to 200 mg a day.

The patent for this brand-name drug expired in June 2006.[14] The drug is now available in generic form in the United States. The generic version of the drug is being produced by Israeli drug maker Teva Pharmaceutical Industries Ltd.[15] In Scandinavia a generic drug called Sertralin, manufactured by HEXAL, is available. The price differences between Zoloft and Sertralin are as much as 1.50 dollars per pill. In India, this drug is sold under the name Zosert.

Green Technology?

In 2002, Pfizer, inc. received an award from the U.S. Environmental Protection Agency, specifically in relation to the manufacture of Sertraline. According to the EPA, Pfizer introduced methods of production that reduced necessary inputs of raw materials and allowed for a reduction of toxic waste. These new methods have been described as more energy-efficient, permitting the company to multiply Sertraline production two-fold. Further, the application of this new process is purportedly safer for workers.[16]

Precautions

- Liver impairment can affect the elimination of this drug from the body. If someone with liver impairment is treated with sertraline, lower or less frequent dosage should be used.
- Patients should limit their alcohol intake while on sertraline (or any antidepressant). Because the liver is doubly taxed with processing both substances (in addition to any other drugs the patient may be taking), alcohol remains in the bloodstream longer, so the effects of alcohol may be more strongly and quickly felt by people taking sertraline or other antidepressants.
- According to some studies grapefruit juice might interfere with the metabolisation of sertraline, increasing its concentration in the blood.
- People 80 years or older should be started on 25 mg initial dose.

Dopamine

Sertraline appears to also be a minor dopamine reuptake inhibitor. At higher dosages (300 mg/day), sertraline inhibits the reuptake of dopamine as well as serotonin.

Controversy

In June 2003, Britain banned sertraline's use for patients under 18 years of age after studies showed a link to increasing suicidal rates. Similar concern has prevailed in the United States, where only the anti-depressant fluoxetine (another SSRI) was officially banned by the FDA for the treatment of depression in minors. However, because the antidepressant-suicide link is correlational, scientists do not know whether the increased suicide risk for people taking antidepressants occurs because the drugs make people suicidal, whether suicide occurs because the drugs un-depress the people enough to motivate the energy required to commit suicide (a popular theory), whether people statistically more likely to commit suicide are over-represented among takers of Zoloft, or because of a fourth, unknown factor.

The brand-name form of setraline, Zoloft, was widely advertised to consumers as "correcting a chemical imbalance", a claim not found in the FDA-approved product labeling. Hundreds of millions of dollars were spent promoting Zoloft this way while it was still on-patent. Some have argued that this advertising may lead consumers to believe that they must take Zoloft to recover when in fact they may benefit from other non-medical treatments such as psychotherapy or exercise.[17]

In the case of Hawkins v The Commonwealth (an Australian court case from the state of New South Wales), Zoloft was described as an important factor in Hawkins murder (through strangling) of his wife. Hawkins had been depressed, was prescribed 50 mg of Zoloft a day and on his first day of treatment took 250 mgs. He claimed on the night of the murder that he couldn't sleep, was agitated and claimed he had hallucinations during the attack on his wife. As a result of this case Zoloft received a large amount of negative publicity, with questions being raised about its impact on behaviour. [1]

Discontinuation Syndrome

Zoloft, along with other SSRIs, has been associated with a "cessation syndrome." This syndrome has both somatic and psychological elements, although SSRIs fall short of being classified as addictive. This non-addictive classification stems from the fact persons given the drug will not seek it out in ever-increasing quantities. Although Zoloft is defined as non-habit forming, the existence of SSRI discontinuation syndrome often necessitates a gradual tapering of one's prescribed dose when seeking to stop SSRI therapy. The prescription insert for Zoloft describes the potential side effects SSRI discontinuation as follows:

"During marketing of Zoloft and other SSRIs and SNRIs (Serotonin and Norepinephrine Reuptake Inhibitors), there have been spontaneous reports of adverse events occurring upon discontinuation of these drugs, particularly when abrupt, including the following: dysphoric mood, irritability, agitation, dizziness, sensory disturbances (e.g. paresthesias such as electric shock sensations), anxiety, confusion, headache, lethargy, emotional lability,

insomnia, and hypomania. While these events are generally self-limiting, there have been reports of serious discontinuation symptoms."[18]

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Serotonin-norepinephrine reuptake inhibitor

Serotonin-norepinephrine reuptake inhibitors (SNRIs) are a class of antidepressant used in the treatment of clinical depression and other affective disorders. They are also sometimes used to treat anxiety disorders, obsessive-compulsive disorder, attention deficit hyperactivity disorder (ADHD) and chronic neuropathic pain. They act upon two neurotransmitters in the brain that are known to play an important part in mood, namely, serotonin and norepinephrine. This can be contrasted with the more widely-used selective serotonin reuptake inhibitors (SSRIs), which act only on serotonin.

The abbreviation "SNRI" should not be used for "'selective' norepinephrine reuptake inhibitors".

Mode of action

Activity on norepinephrine reuptake is thought necessary for an antidepressant to be effective on neuropathic pain, a property shared with the older tricyclic antidepressants but not with the SSRIs.

Depression is thought to be caused by a lack of information flow between neurons in certain parts of the brain. Neurons pass information to each other by means of chemicals known as neurotransmitters, which shoot across the tiny synapses between the cells. After firing, most of the neurotransmitter is reabsorbed by the presynaptic cell in a process called reuptake.

Antidepressants work by increasing the amount of neurotransmitters active in the synapse, thereby enhancing neuronal activity and increasing the responsiveness of mood. Modern antidepressants usually achieve this effect by blocking the transporter proteins that reabsorb certain neurotransmitters, hence the name "reuptake inhibitors".

SNRIs were developed more recently than SSRIs, and there are relatively few of them. Their efficacy as well as their tolerability appears to be somewhat better than the SSRIs, owing to their compound effect. Norepinephrine, epinephrine, dopamine and serotonin are

monoamine neurotransmitters subdivided into two groups catecholamines and indolamines. Serotonin is the only indolamine as its synthesised from amino acid tryptophan

Adverse effects

As with the SSRIs, abrupt discontinuation of SNRI-medication usually leads to a discontinuation syndrome which could include states of anxiety and further symptoms. It is therefore recommended to slowly taper down the dose under the supervision of a psychopharmacologist when discontinuing SNRIs.

SNRIs currently available

- *venlafaxine* (tradenames *Effexor XR*®, *Efexor*®) is the first and most commonly used SNRI. Although it also works on dopamine somewhat at high dosages, the majority of its effect is on serotonin and norepinephrine.
- *nefazodone* (tradename *Serzone*®) is an antidepressant with efficacy similar to SSRIs, but without the sexual side effects. In fact, Serzone at times may act similarly to Wellbutrin in its neutral or at times positive effect on function. It has been discontinued in several countries due to rare cases of liver failure. The tradename "Serzone®" has been discontinued, however generic nefazodone is currently available (May 06). However, the liver failure is rare, and a simple blood test every 6 months to assess liver enzyme levels is sufficient. Nefazodone has an active metabolite which at higher doses (> 250mg/day) can increase anxiety. One of the benefits nefazodone has over *Effexor*® and *Cymbalta*® is its enhanced sedation when taken at bedtime.
- *milnacipran* (tradename *Dalcipran*®*/ Portugal*; *Ixel*®*/ France*) has shown to be significantly effective in the treatment of depression and Fibromyalgia syndrome (FMS). Although it has not yet been approved by the Food and Drug Administration (FDA) for use in the United States, it has been commercially available in Europe and Asia for several years.
- *desipramine* (tradenames *Norpramine*®, *Pertofraneis*®) is technically a tricyclic antidepressant, and is usually categorized as such. It works, however, on both serotonin and norepinephrine, so it can also be considered an SNRI.
- *duloxetine* (tradename *Cymbalta*®) by Eli Lilly and Company, also inhibits serotonin and has been approved for the treatment of depression and neuropathic pain in August of 2004.

Please note that some of the above medications may not be considered "true" SNRIs; refer to specific peer-reviewed scientific journals for more in-depth coverage on classifications and pharmaco-kinetics.

Selective serotonin reuptake enhancers

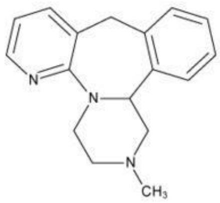
Selective serotonin reuptake enhancers (SSREs) are antidepressants that enhance the reuptake of serotonin instead of blocking it.

Examples of selective serotonin reuptake enhancers include:

- Tianeptine (INN) (Stablon®, Coaxil®, Tatinol®)

Tetracyclic antidepressants

There are also several chemically unrelated tetracyclic antibiotics based on Tetracycline.


The structure of the tetracyclic antidepressant mirtazapine

A *tetracyclic antidepressant* is an antidepressant drug from the tetracyclic drug group.

The name tetracyclic is derived from the drug's molecular structure which consists of four ring-like structures in a T-shape (compare tricyclic antidepressant).

Maprotiline, trade named *Ludiomil*®, and Mirtazapine, trade named *Remeron*® in the USA, *Zispin*® in Europe and *Avanza*® in Australia, are the only two drugs from this group widely used for the treatment of clinical depression. The tetracyclic antidepressant Mianserin was previously available internationally, however in most markets it has been phased out in favor of Mirtazapine.

Research on other tetracyclic antidepressant compounds (for example setiptiline) have been reported in the scientific literature. These other tetracyclic antidepressants are not publicly available.

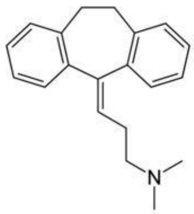
List of tetracyclic antidepressants

- Amoxapine
Maprotiline
Mianserin
Mirtazapine
Nefazodone
Setiptiline
Trazodone

External links

- FPnotebook PSY193

Tricyclic antidepressants



Chemical structure of the tricyclic antidepressant amitriptyline.

Tricyclic antidepressants are a class of antidepressant drugs first used in the 1950s. They are named after the drugs' molecular structure, which contains three rings of atoms (compare tetracyclic antidepressant). The term 'tricyclic antidepressant' is sometimes abbreviated to *TCA*.

Mechanism of action

The exact mechanism of action is not well understood, however it is generally thought that tricylic antidepressants work by inhibiting the re-uptake of the neurotransmitters norepinephrine, dopamine, or serotonin by nerve cells. Tricyclics may also posses an affinity for muscarinic and histamine H1 receptors to varying degrees. Although the pharmacologic effect occurs immediately, often the patient's symptoms do not respond for 2 to 4 weeks.[1]

Clinical use

Tricyclic antidepressants are used in numerous applications; mainly indicated for the treatment of clinical depression, pain, nocturnal enuresis, and ADHD, but they have also been used successfully for headache, bulimia nervosa, interstitial cystitis, irritable bowel syndrome, narcolepsy, persistent hiccups, pathological crying or laughing, smoking cessation, as an adjunct in schizophrenia, and in ciguatera poisoning.[1]

Depression

For many years they were the first choice for pharmacological treatment of depression. Although still considered effective, they have been increasingly replaced by SSRIs and other newer drugs. These newer antidepressants are thought to have fewer side effects and are also thought to be less effective if used in a suicide attempt, as the treatment and lethal doses (see therapeutic index) are farther apart than with the tricyclic antidepressants. Tricyclic antidepressants are sometimes still used to treat refractory depression that has failed to respond to standard SSRI therapy.[2] They are not considered addictive and are preferable to the MAOIs. Side effects usually occur before depression is effectively suppressed; for this reason and via other mechanisms they can be dangerous, as volition may be increased, giving the patient greater ability to attempt suicide.[3]

ADHD

Tricyclic antidepressants have been shown to be effective in treating attention-deficit hyperactivity disorder.[4] ADHD is thought to be caused by dopamine and norepinephrine shortages in the brain's prefrontal cortex. Tricyclic antidepressants block the reuptake of these neurotransmitters, thus acting as dopamine and norepinephrine agonists.[5] They are commonly used in patients for whom psychostimulants (the primary medication for ADHD) are ineffective. TCAs are more effective in treating the behavioral aspects of ADHD than the cognitive deficits; they help limit hyperactivity and impulsivity but have little effect on attention.[6]

Analgesia

Tricyclics are also known as effective analgesics for different types of pain, especially neuropathic or neuralgic pain (like back pain in radiculitis).[7][8] A precise mechanism for their analgesic action is unknown, but it is thought that they modulate opioid systems in the CNS via an indirect serotonergic route.[9] Typically pain modification requires lower dosages than for treating depression (e.g. Amitriptyline at 10 to 30 mg rather than 75 to 150 mg). They are also effective in migraine prophylaxis, but not in relief of an acute migraine attack. This is also believed to be related to serotonergic effects. There is, however, little evidence for an analgesic effect in acute pain.[1]

Nocturnal enuresis

Tricyclics with greater anti-muscarinic action (i.e., amitriptyline, imipramine and nortriptyline) may prove useful in helping to treat nocturnal enuresis (bedwetting) in children over the age of 7 years. The drug needs to be gradually withdrawn and the total treatment period is advised to be no greater than 3 months at a time. It is thought that the anticholinergic effects of tricyclics may inhibit urination, and/or the CNS stimulant effect may lead to easier arousal when the stimulus of a full bladder occurs.[10] However, one robust review of tricyclics for the treatment of enuresis found the benefits of tricyclics were relatively small and transient and due to potentially serious adverse effects suggested more research into other methods (bedwetting alarms, behavioural methods, desmopressin) which may be better suited for treatment of this condition.[11]

Side effects

Many side effects are related to tricyclics antimuscarinic actions. The antimuscarinic side effects are relatively common and include:

- Dry mouth (salivary secretion is affected)
- Blurred vision (accommodation in the eye is affected)
- Decreased gastro-intestinal motility and secretion. This may lead to constipation
- Urinary retention or difficulty with urination

- Hyperthermia

Tolerance to the these adverse effects often develops if treatment is continued, side effects may also be less troublesome if treatment is initiated with low dose and then gradually increased, although this may delay the clinical effect.

Other side effects may include drowsiness, anxiety, restlessness, cognitive and memory difficulties, confusion, dizziness, akathisia, hypersensitivity reactions, increased appetite with weight gain, sweating, decrease in sexual ability and desire, muscle twitches, weakness, nausea and vomiting, hypotension, tachycardia, and rarely, irregular heart rhythms.[1]

Interactions

TCAs are highly metabolized by the cytochrome P450 hepatic enzymes. Drugs that inhibit cytochrome P450 (for example cimetidine, methylphenidate, antipsychotics, and calcium channel blockers) may produce decreases in the tricyclics metabolism leading to increases in tricyclic blood concentrations and accompanying toxicity. Drugs which prolong the QT interval including antiarrythmics such as quinidine, the antihistamines astemizole and terfenadine, and some antipsychotics may increase the chance of ventricular dysrhythmias. TCAs may enhance the response to alcohol and the effects of barbiturates and other CNS depressants. Side effects may also be enhanced by other drugs which have antimuscarinic properties.[1]

Overdose

Tricyclic antidepressant overdose is a significant cause of fatal drug poisoning. The severe morbidity and mortality associated with these drugs is due to their well documented cardiovascular and neurological toxicity. Additionally, they are a serious problem in the pediatric population due to their inherent toxicity[12] and the availability of these in the home when prescribed for bed wetting and depression.

Symptoms

The central nervous system and heart are the two main systems that are affected. Initial or mild symptoms include drowsiness, a dry mouth, nausea, and vomiting. More severe complications, include hypotension, cardiac rhythm disturbances, hallucinations, and seizures. Electrocardiogram (ECG) abnormalities are frequent and a wide variety of cardiac dysrhythmias can occur, the most common being sinus tachycardia and intraventricular conduction delay (QRS prolongation).[13] Seizures and cardiac dysrhythmias are the most important life threatening complications.

Toxicity

Tricyclics have a narrow therapeutic index, i.e. the therapeutic dose is close to the toxic dose. In the medical literature the lowest reported toxic dose is 6.7 mg per kg body weight, ingestions of 10 to 20 mg per kilogram of body weight are a risk for moderate to severe

poisoning, although doses ranging from 1.5 to 5 mg/kg may even present a risk. Most poison control centers refer any case of TCA poisoning (especially in children) to a hospital for monitoring.[14] Factors that increase the risk of toxicity include advancing age, cardiac status, and concomitant use of other drugs.[15] Serum drug levels are not useful in tricyclic overdose.[16]

Toxic mechanism

Most of the toxic effects of TCAs are caused by four major pharmacological effects. TCAs have anticholinergic effects, cause excessive blockade of norepinephrine reuptake at the postganglionic synapse, direct alpha adrenergic blockade, and importantly they block sodium membrane channels with slowing of membrane depolarization, thus having quinidine like effects on the myocardium.[17]

Treatment

Initial treatment of an acute overdose includes gastric decontamination of the patient. This is achieved by administering activated charcoal which adsorbs the drug in the gastrointestinal tract either orally or via a nasogastric tube. Other decontamination methods such as stomach pumps, ipecac induced emesis, or whole bowel irrigation are not recommended in TCA poisoning.[18][19]

Symptomatic patients are usually monitored in an intensive care unit for a minimum of 12 hours, with close attention paid to maintenance of the airways, along with monitoring of blood pressure, arterial pH, and continuous ECG monitoring.[17] Supportive therapy is given if necessary, including respiratory assistance, maintenance of body temperature, and administration of sodium bicarbonate as an antidote. Sodium bicarbonate is given intravenously and it has been shown to be an effective treatment for resolving the metabolic acidosis and cardiovascular complications of TCA poisoning. If sodium bicarbonate therapy fails to improve cardiac symptoms, conventional antidyshythmic drugs such as phenytoin and magnesium can be used to reverse any cardiac abnormalities. However, no benefit has been shown from lidocaine or other class 1a and 1c antiarrhythmic drugs; it appears they worsen the sodium channel blockade, slow conduction velocity, and depress contractility and should be avoided in TCA poisoning.[20] Hypotension is initially treated with fluids along with bicarbonate to reverse metabolic acidosis (if present), if the patient remains hypotensive despite fluids then further measures such as the administration of epinephrine, norepinephrine, or dopamine can be used to increase blood pressure.[20] Another potentially severe symptom is seizures; often seizures resolve without treatment but administration of a benzodiazepine or other anticonvulsive may be required for persistent muscular overactivity. There is no role for physostigmine in the treatment of tricyclic toxicity as it may increase cardiac toxicity and cause seizures.[17]

Tricyclic antidepressants are highly protein bound and have a large volume of distribution; therefore removal of these compounds from the blood with hemodialysis, hemoperfusion or other techniques are unlikely to be of any significant benefit.[19]

Epidemiology

Studies in the 1990s in Australia and the United Kingdom showed that between 8 and 12% of drug overdoses were following TCA ingestion. TCAs may be involved in up to 33% of all fatal poisonings, second only to analgesics.[21][22]

Example compounds

The first tricyclic antidepressant discovered was imipramine, which was discovered accidentally in a search for a new antipsychotic in the late 1950s.

Antidepressant drugs in the tricyclic drug group include:

- amitriptyline (Elavil®, Endep®, Tryptanol®, Trepiline®)

clomipramine (Anafranil®)
desipramine (Norpramin®, Pertofrane®)
dothiepin hydrochloride (Prothiaden®, Thaden®)
doxepin (Adapin®, Sinequan®)
imipramine (Tofranil®)
lofepramine (Gamanil®, Lomont®)
nortriptyline (Pamelor®)
protriptyline (Vivactil®)
trimipramine (Surmontil®)

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See also

- Antidepressant

- Tetracyclic antidepressant

Anxiolytics

An *anxiolytic* is a drug prescribed for the treatment of symptoms of anxiety. Some anxiolytics have been shown to be useful in the treatment of anxiety disorders as have antidepressants such as the class of selective serotonin reuptake inhibitors (SSRIs).

Though not anxiolytics, beta-receptor blockers such as propranolol and oxprenolol can be used to combat the somatic symptoms of anxiety.

Types of anxiolytics

Anxiolytics are generally divided into two groups of medication, benzodiazepines and non-benzodiazepines. There are also herbal treatments used, though research into their efficacy and safety is limited.

Benzodiazepines

- Main article: Benzodiazepine

Benzodiazepines are prescribed for short-term relief of severe and disabling anxiety. Common medications are lorazepam (Ativan®), alprazolam (Xanax®), and diazepam (Valium®). Benzodiazepines may also be indicated to cover the latent periods associated with the medications prescribed to treat an underlying anxiety disorder. They are used to treat a wide variety of conditions and symptoms and are usually a first choice when short-term CNS sedation is needed. Longer term uses include severe anxiety and psychosis. There is a risk of withdrawal symptoms and rebound syndrome after continuous usage past two weeks. There is also the added problem of the accumulation of drug metabolites and adverse effects.

Non-benzodiazepines

Buspirone (Buspar®) is a serotonin 1A agonist. It lacks the sedation and the dependence associated with benzodiazepines and causes much less cognitive impairment. It may be less effective than benzodiazepines in patients who have been previously treated with benzodiazepines as the medication does not provide the euphoria and sedation that these patients may expect or equate with anxiety relief.

Barbiturates and meprobamate exert an anxiolytic effect linked to the sedation they cause. The risk of abuse and addiction is high. Many experts consider these drugs as obsolete for treating anxiety, although they may be valuable for the short term treatment of severe insomnia.

Herbal treatments

Certain herbs, such as St. John's wort and kava (kava kava), have been used as anxiolytics, but limited reliable evidence is available for their efficacy. In Europe, the root of the valerian is also popular as an anxiolytic.

Alternatives to medication

Psychotherapy (e.g. cognitive or behavior therapy) is often useful as an adjunct to pharmacotherapy or as an alternative to medication.

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Cannabis

Scientific classification

Kingdom: Plantae
Division: Magnoliophyta
Class: Magnoliopsida
Order: Rosales
Family: Cannabaceae
Genus: *Cannabis* L.

Species Cannabis sativa L

Cannabis is a genus of flowering plant that includes one or more species. The plant is believed to have originated in the mountainous regions just north-west of the Himalayas. It is also known as hemp, although this term usually refers to varieties of Cannabis cultivated for non-drug use. Cannabis plants produce a group of chemicals called cannabinoids which produce mental and physical effects when consumed. As a drug it usually comes in the form of dried flowers and leaves (marijuana), resin (hashish), or various extracts collectively known as hash oil [1]. In the early 20th century, it became illegal in most of the world to cultivate or possess Cannabis for drug purposes.

Species

Cannabis sativa L

Putative species or subspecies:

    - C. indica Lam. = C. sativa L subsp. indica (Lam.) E. Small & Cronquist
- C. ruderalis Janisch. = C. sativa subsp. sativa var. spontanea Vav. = C. sativa L subsp. sativa

Description

Cannabis is a dioecious annual flowering herb. Cannabis usually has imperfect, unisexual flowers; the male (staminate) reproductive structures are completely separate from the female (carpellate, sometimes called pistillate) structures, [2] [3] although sometimes perfect hermaphrodite flowers also occur.[4] Cannabis is dioecious [2], which means that entire plants usually bear only male or only female flowers, with male flowers borne on loose panicles, and female flowers borne on racemes.[5] However it is not unusual for individual plants to bear both male and female flowers, a condition called monoecy. [6] Flowers of both sexes sometimes occur on separate inflorescences, or sometimes within the same inflorescence. [4] Dense clusters of female flowers produced by drug varieties of Cannabis are commonly called "buds" although in this usage the term refers to clusters of mature flowers, rather than the undeveloped shoots that the word ordinarily describes.

All varieties of Cannabis are wind-pollinated [2] [7] and produce seeds that are called nuts [2] or achenes. [8]. Most varieties of Cannabis are short day plants [7], with the exception of C. sativa subsp. sativa var. spontanea (syn. C. ruderalis), which is commonly described as "auto-flowering" and may be either day-neutral or require long days.

Cannabis is used as a food plant by the larvae of some Lepidoptera species including Ghost Moth and The Nutmeg.

Taxonomy

The genus Cannabis was formerly placed with nettles in the family Urticaceae or with mulberries in the family Moraceae, but is now considered along with hops (Humulus sp.) to belong to the family Cannabaceae.

All strains of Cannabis can interbreed, and produce fertile offspring, which means that all known Cannabis plants satisfy one criterion for a single species type called Cannabis sativa L.[9]. But whether the different strains of Cannabis actually do constitute a single species or multiple species has been a contentious issue for more than two centuries.[10][11][12][13][14]

Early classifications

Cannabis was first classified by Carolus Linnaeus in 1753 as a genus comprising a single species, called Cannabis sativa, describing hemp, which was widely cultivated at the time. In 1785, famous French biologist Jean-Baptiste Lamarck described C. indica, a type of Cannabis from India having morphological distinctiveness from the C. sativa previously described, and in particular not suitable for use as hemp because of poor fiber quality, but having greater potential as an inebriant. Numerous additional species were proposed in the 19th century, but by the beginning of the 20th century, the single-species concept was widely

accepted.[5][10], except within the Soviet Union, where Cannabis continued to be the subject of active taxonomic study.

20th Century

In 1924, Janischevsky described the low-intoxicant type of wild (ruderal) Cannabis found in central Russia as either a species or a variety, proposing C. ruderalis or C. sativa var. ruderalis as alternative names.[10] In 1929, Vavilov described wild populations of drug-type Cannabis as the variiety C. indica var kafiristanica, and recognized the wild populations previously described by Janischevsky as the variety C. sativa L subsp sativa var. spontanea Vav. [14][15][11] In 1940, Serebriakova and Sizov proposed a classification of Cannabis recognizing C. sativa L and C. indica Lam. as distinct species, describing "common hemp" and "Indian hemp" respectively. Within common hemp, they recognized cultivated and wild populatins as distinct subspecies, C. sativa var. culta and C. sativa var spontanea. They additionally recognized a total of 17 varieties within C. sativa, including 4 distinct groups within the cultivated subspecies, but did not describe variation within C. indica.[10]

In the late 1960's and 1970's, the question of scientific classification of Cannabis took on legal importance in North America. Laws prohibiting Cannabis in the United States and Canada specifically named products of Cannabis sativa L. as the prohibited substances. Several persons charged with violating these laws claimed that the material was in fact derived from C. indica or C. ruderalis, and was therefore not prohibited by the laws. Legal defenses on this basis were not often successful. [14]

In the early 1970's, botanists Richard E. Schultes and Loran Anderson conducted taxonomic studies of Cannabis, and concluded that sufficient evidence exists to support recognition of three species, C. sativa L, C. indica Lam., and C. ruderalis Janisch. [16][17] For Schultes, this was a reversal of his previous opinion that Cannabis is a monotypic genus. [10] According to their species descriptions, C. sativa is tall and laxly branched with relatively narrow leaflets, C. indica is shorter, conical in shape, and has relatively wide leaflets, and C. ruderalis is short, branchless, and grows wild in central Asia. This concept was embraced by Cannabis aficionados who commonly distinguish narrow-leafleted "sativa" drug strains from wide-leafleted "indica" drug strains.

In 1976, Ernest Small and Arthur Cronquist proposed a classification comprising a single species Cannabis sativa L, with two subspecies: C. sativa L subsp. sativa and C. sativa L subsp. indica (Lam). According to this concept, C. sativa subsp. sativa was selected for traits that enhance fiber or seed production and has low levels of the psychoactive delta-9-tetrahydrocannabinol (THC), whereas C. sativa subsp. indica was primarily selected for drug production and has relatively high levels of THC. Within these subspecies they described C. sativa L subsp. sativa var. spontanea (Vav.) as a wild or escaped type of low-intoxicant Cannabis, and described C. sativa L subsp. indica var. kafiristanica (Vav.) as a wild or escaped variety of the high-intoxicant type. [11]. This classification was based on several factors, including interfertility, chromosome uniformity, systematic chemotype analysis, and numerical analysis of diagnostic characters. [11][18]. [19] Ernest Small was awarded the G. M. Cooley Prize by the American Association of Plant Taxonomists for his work involving Cannabis. [20]

Ongoing research

Molecular analytical techniques developed in the late twentieth century are being brought to bear on questions of scientific classification. This has resulted in many reclassifications based on evolutionary systematics. Scientific classification of Cannabis has been investigated using molecular biology and genetic techniques.

Several groups conducted genetic analyses of RAPD markers among drug and fiber cultivars. These analyses showed an extremely high degree of genetic polymorphism between and within populations, suggesting a very high degree of potential variation, even in heavily selected cultivars. [21] [22][23] Long-time Cannabis researcher EPM de Meijer described these analyses as confirming the continuity of the gene pool throughout the studied accessions, and as further confirmation that the genus comprises a single species. [24]

In 2004, Karl W. Hillig, then a postgraduate student at Indiana University teamed with Cannabis expert[25] Paul Mahlberg to conduct a chemotaxomic analysis of Cannabis, using analytical chemistry of cannabinoid content to determine allele frequencies within studied populations. They concluded that observed chemotypes support recognition of C. sativa and C. indica as distinct species, but concluded that recognition of C. ruderalis was not supported but rather was consistent with classification of C. ruderalis as C. sativa var spontanea Vav. The authors categorized fiber/seed landraces and feral populations from Europe, central Asia, and Asia Minor in C. sativa., and categorized narrow-leaflet drug (NLD), wide-leaflet drug (WLD) cultivars, southern and eastern Asian hemp cultivars, and feral Himalayan populations as C. indica. [15] In 2005, Hillig published another paper based on the same research, with additional statistical analyses, and this time proposed a 3-species classification, recognizing C. sativa, C. indica, and C. ruderalis.[26] In his doctoral dissertation, published the same year, Hillig stated that principal components analysis failed to differentiate the putative species, but that canonical variates analysis resulted in a high degree of discrimination of the putative species and infraspecific taxa. Hillig stated that the patterns of variation support a two-species concept, but not recognition of C. ruderalis as a separate species from C. sativa. His conclusion was that taxonomic revision of Cannabis is warranted, but further research is needed to substantiate his proposed taxonomic treatment. [27]

As of 2006, the single-species concept of Cannabis continues to be widely accepted. [28][29][30][31][24][32][33]

Popular usage

Breeders, seed companies, and cultivators of drug type Cannabis often describe the ancestry or gross phenotypic characteristics of cultivars by categorizing them as pure indica, mostly indica, indica/sativa, mostly sativa, or pure sativa.[34]

In September of 2005, New Scientist reported that researchers at the Canberra Insitute of Technology had identified a new subspecies of Cannabis, based on analysis of mitochondrial and chloroplast DNA. [35]. The New Scientist story, which was picked up by many news agencies and web sites, indicated that the research was to be published in the

journal Forensic Science International. As of November 2006, the work has not appeared in that journal.

Geographical distribution

Wild cannabis

Wild C. sativa subsp. indica is mainly confined to hash producing areas such as Afghanistan, and parts of Morocco. Wild C. sativa subsp. sativa shows great local variation; for example, in warm places, it can reach heights up to 20 feet (6 m) tall, but in colder climates it can be as short as 1 foot (30 cm) in height. Almost every single flower branch bears a seed. The wild C. sativa subsp. sativa has long, thin and airy buds and a Christmas tree shape structure. Wild C. sativa subsp. indica remains compact and bushy with thick buds for the most part, and is sometimes used by the locals for hashish production. Generally, there are far fewer seeds in wild C. sativa subsp. indica.

In many areas, wild or naturalized populations of Cannabis are considered invasive species, and are often targeted by government-sponsored eradication programs.

Reproduction

Breeding systems

Cannabis has been described as predominantly dioecious [2][7][36], although some monoecious varieties have also been described [37] Subdioecy (the occurrence of monoecious individuals and dioecious individuals within the same population) is widespread. [6][38][39] Many populations have been described as sexually labile. [40][41][23]

As a result of intensive selection in cultivation, Cannabis exhibits many sexual phenotypes, which can be described in terms of the ratio of female to male flowers occurring in the individual or typical in the cultivar[42]. Dioecious varieties are preferred for drug production, where the female plants are preferred. Dioecious varieties are also preferred for textile fiber production, whereas monecious varieties are preferred for pulp and paper production. It has been suggested that the presence of monoecy can be used to differentiate between licit crops of monoecious hemp and illicit dioecious drug crops. [6]

Mechanisms of sex determination

Cannabis has been described as having one of the most complicated mechanisms of sex determination among the dioecious plants.[42] Many models have been proposed to explain sex determination in Cannabis.

Based on studies of sex reversal in hemp, it was first reported in 1924 by K. Hirata that an XY sex-determination system is present.[40] At the time, the XY system was the only known system of sex determination. The X:A system was first described in Drosophila spp in 1925.[43] Soon thereafter, Schaffner disputed Hirata's interpretation,[44] and published

results from his own studies of sex reversal in hemp, concluding that an X:A system was in use and that futhermore sex was strongly influenced by environmental conditions.[41]

Since then, many different types of sex determination system have been discovered, particularly in plants[36]. Dioecy is relatively uncommon in the plant kingdom, and a very low percentage of dioecious plant species have been determined to use the XY system. In most cases where the XY system is found it is believed to have evolved recently and independently.[45]

Since the 1920's, a number of sex determination models have been proposed for Cannabis. Ainsworth[36] describes sex determination in the genus as using "an X/autosome dosage-type."

The question of whether heteromorphic sex chromosomes are indeed present is most conveniently answered if such chromosomes were clearly visible in a karyotype. Cannabis was one of the first plant species to be karyotyped, however, this was in a period when karyotype preparation was primitive by modern standards. Heteromorphic sex chromosomes were reported to occur in staminate individuals of dioecious 'Kentucky' hemp, but were not found in pistillate individuals of the same variety. Dioecious 'Kentucky' hemp was assumed to use an XY mechanism. Heterosomes were not observed in analyzed individuals of monoecious 'Kentucky' hemp, nor in an unidentified German cultivar. These varieties were assumed to have sex chromosome composition XX. [37] But according to other researchers no modern karyotype of Cannabis had been published as of 1996.[46] Proponents of the XY system state that Y chromosome is slightly larger than the X, but difficult to differentiate cytologically. [47]

More recently, Sakamoto and various co-authors[48][49] have used RAPD to isolate several genetic marker sequences that they name Male-Associated DNA in Cannabis (MADC), and which they interpret as indirect evidence of a male chromosome. Several other research groups have reported identification of male-associated markers using RAPD and AFLP[50][23][24]. Ainsworth commented on these findings, stating that "It is not surprising that male-associated markers are relatively abundant. In dioecious plants where sex chromosomes have not been identified, markers for maleness indicate either the presence of sex chromosomes which have not been distinguished by cytological methods or that the marker is tightly linked to a gene involved in sex determination." [36]

Environmental sex determination is known to occur in a variety of species.[51] Many researchers have suggested that sex in Cannabis is determined or strongly influenced by environmental factors [41]. Ainsworth reviews that treatment with auxin and ethylene have feminizing effects, and that treatment with cytokinins and gibberellins have masculinizing effects.[36] It has been reported that sex can be reversed in Cannabis using chemical treatment.[52]

Aspects of cannabis production and use

- Medical cannabis discusses its use as a medication.

Cannabis (drug) discusses its use as a recreational drug.

Spiritual use of cannabis discusses sacramental and religious use.

Hemp discusses its uses as a source of housing, oil, food, fibers, and industrial materials.

Cannabis (drug) cultivation discusses aspects of cultivation for medicinal and recreational drug purposes

Legal issues of cannabis focuses on the law and enforcement aspects of growing, transporting, selling and using cannabis as a drug.

Health issues and the effects of cannabis discusses the pharmacology, physical, and mental effects of Cannabis when used as drug.

Etymology

The plant name *cannabis* is probably of Semitic origin, possibly Hebrew.

Hebrew ç°àµÔ Ñ¹¼é¶ÂÝ *qnh bo[em* > ç·à·¼Ñ¼Õ¹á *qannabbôs* > Greek º±½½±²¹Â *kannabis* > Latin *cannabis* > English

However, the earlier Sumerian language used the word "kanubi", which means 'cane of two (sexes?)'. This is possibly the source for the Semitic usage.

The Biblical Hebrew term qnh bo[em, literally "reed of balm", probably [53] refers to cannabis according to some etymologists [54], but is more commonly thought to be lemon grass, calamus , or even sweet cane, due to widespread translation issues. [55] The Hebrew Bible mentions it in Exodus 30:23 where God commands Moses to make a holy oil of myrrh, cinnamon, qnh bo[em and cassia to anoint the Ark of the Covenant and the Tabernacle (and thus God's Temple in Jerusalem). Notably, this anointing oil is a special herbal formula that functions as a kind of polish and fragrance for the Ark and Tabernacle, and the Bible forbids its manufacture and use to anoint people (Exodus 30:31-33) with the exception of the Aaronic priesthood (Exodus 30:30)

Elsewhere, the Hebrew Bible simply uses "reed" qnh as the name of a plant in four places whose context seems to mean "reed of balm" as a fragrant resin, Isaiah 43:24, Jeremiah 6:20, Ezekiel 27:19 and Song of Songs 4:14. The Hebrew name "reed of balm" comes from qnh (the noun construct form of qneh) means a "reed" or "cane" and bo[em means "balm" or "aromatic" resin. Hebrew may have adapted the name qannabbôs from "reed of balm" qnh bo[em as a substitute for the ambiguous name "reed".

This Biblical Hebrew term is often mistranslated as "calamus", also called "lemon grass" (Cymbopogon citratus) or "sweet flag" (Acorus calamus), following an ancient misunderstanding in the Greek Septuagint translation. The Hebrew Bible was written across centuries well up to the 5th Century BCE. However, centuries later, by the time the Septuagint was written around the 2nd Century BCE, the archaic Hebrew word qnh bo[em appears to have already abbreviated into the later Hebrew form qannabbôs, which is attested in Post Biblical Hebrew literature. Thus, the Septuagint did not recognize the Hebrew expression "reed of balm" and mistook it to refer to some unidentified plant. As a dynamic equivalent, the Septuagint rendered it as "calamus" (Greek kalamos), which indeed is a "balmy" (scented) reed. The calamus plant was known in Greek mythology and processed into an aphrodisiac.

Unambiguous Hebrew or Aramaic references to cannabis are rare and obscure. Syriac has qanpa (a loan from kannabis) and tanuma (see the Comprehensive Aramaic Lexicon.) but neither is found in the Peshitta, the Syriac Bible. Late Syriac Ahiqar texts include qanpa as "ropes of hemp" (tunbei de-qanpa). The Hebrew word qanbes, a loan word from kannabis,

is used in the Mishnah as hemp [Kilaim 2:5; 5:8; 9:1,7; Negaim 11:2] in the sense of a constituent of clothing or other items.

The Scythian term cannabis probably derives from a Semitic origin as well. Sara Benetowa of the Institute of Anthropological Sciences in Warsaw is quoted in the Book of Grass as saying:

> The astonishing resemblance between the Semitic *kanbos* and the Scythian *cannabis* lead me to suppose that the Scythian word was of Semitic origin. These etymological discussions run parallel to arguments drawn from history. The Iranian Scythians were probably related to the Medes, who were neighbors of the Semites and could easily have assimilated the word for hemp. The Semites could also have spread the word during their migrations through Asia Minor.

Likely, the name 'cannabis' was known from the Semitic merchants who sold this commodity throughout the ancient trade routes of Southeast Asia.

Comparing the English word hemp and the Greek word kannabis shows that the word came down from the presumed Proto-Indo-European language. Words like kanapish for "hemp" occur in some Finno-Ugrian languages. It is likely that, soon after agriculture started, hemp as a cultivated plant spread widely, carrying its name with it. Source of Rus. konoplja, Pers. kanab, Lith. kanapes "hemp," and Eng. canvas and hemp.

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Cannabis drug

The psychoactive drug *cannabis* is known by many nicknames (some pertaining to certain preparations.) It is produced from parts of the Cannabis sativa plant, primarily the cured flowers and gathered trichomes of the female plant (as well as the less psychoactive remains of the plant, and its highly psychoactive resin.) The major active chemical compound ”9-tetrahydrocannabinol, commonly referred to as THC, has psychoactive and medicinal effects when consumed, usually by smoking or ingestion. Humans have been consuming cannabis since prehistory, though in the 20th century there was a rise in the use of cannabis for recreational and religious purposes. At the beginning of the 21st century, it is estimated that cannabis is used by four per cent of the world's adult population each year, making cannabis more popular than all other illicit drugs combined. [1] The possession, use, or sale of psychoactive cannabis products became illegal in many parts of the world in the early 20th century. Since then, while some countries have intensified the enforcement of cannabis prohibition, others have reduced the priority of enforcement to the point of tolerating consumption. The supplying of cannabis remains illegal almost everywhere in the world through the 1961 Single Convention on Narcotic Drugs, the 1971 Convention on Psychotropic Substances, and the 1988 United Nations Convention Against Illicit Traffic in Narcotic Drugs and Psychotropic Substances, while simple possession of small quantities is tolerated in a few countries.

Ancient history

Biologists generally agree that the natural cannabis plant first grew somewhere in the Himalayas. Evidence of the smoking of cannabis can be found as far back as the Neolithic age, where charred hemp seeds were found in a ritual brazier at a burial site in present day Romania[2] . The most famous users of cannabis were the ancient Hindus. It was called ganjika in Sanskrit (ganja in modern Indian languages).[3] According to legend, Shiva, the

destroyer of evil in the Hindu trinity, told his disciples to revere the plant. The ancient drug soma, mentioned in the Vedas as a sacred intoxicating hallucinogen, was sometimes associated with cannabis. It has also been identified with a number of other plants and a mushroom, Amanita muscaria, so the involvement of cannabis cannot be definitively quantified.

The citizens of the Persian Empire would partake in the ceremonial burning of massive cannabis bonfires, directly exposing themselves and neighboring tribes to the billowing fumes, oftentimes for over 24 hours. [4][5]

Cannabis was also well known to the Assyrians, who discovered it from the Aryans. Using it in some religious ceremonies, they called it qunubu, or the drug for sadness. Also introduced by the Aryans, the Scythians as well as the Thracians/Dacians used it, whose shamans (the kapnobatai - "those who walk on smoke/clouds") burned cannabis flowers in order to induce trances. The cult of Dionysus, which is believed to have originated in Thrace, is also believed to have inhaled cannabis smoke.

Religious and spiritual use

Cannabis has a long history of religious use, especially in India, where it has been used by wandering spiritual sadhus for centuries. The religious group that (in the west) is most well-known for their use of cannabis in a spiritual context is the Rastafari movement, though it is by no means the only group (others include the Church of the Universe). Some historians and etymologists have claimed that cannabis was used by ancient Jews, early Christians, and of early Muslims of the Sufi order.[6] Hashish was said to have been used by the Hashshashin, a warrior sect, but there is no significant evidence for this, as the name was only used as a derogatory term for them by others. [6]

Many individuals also consider their use of cannabis to be spiritual regardless of organized religion.

Medicinal use

Medically, cannabis is most often used as an appetite stimulant and pain reliever for certain illnesses, including cancer, AIDS and other diseases. It is used to relieve glaucoma and certain neurological illnesses such as epilepsy, migraine and bipolar disorder. It has also been found to relieve nausea for chemotherapy patients. A recent study has also indicated that cannabis can be used to prevent Alzheimer's disease[1]. The medical use of cannabis is politically controversial, but physicians sometimes recommend it informally. A synthetic version of the major active chemical in cannabis, THC, is available in many countries in the form of a pill as the prescription drug dronabinol (Marinol). THC has also been found to reduce arterial blockages[7]. A sublingual spray derived from an extract of cannabis has also been approved for treatment of multiple sclerosis in Canada as the prescription drug Sativex [8] - this drug may now be legally imported into the United Kingdom and Spain on prescription.[9]

United States

Eleven states[10] in the United States passed laws allowing cannabis possession and consumption for medical purposes; however, the Supreme Court of the United States in Gonzales v. Raich ruled that the listing of cannabis as a Schedule I controlled substance was constitutional, and that possession for any reason other than approved medical research was therefore illegal under federal law. This remained consistent with their ruling in United States v. Oakland Cannabis Buyers' Cooperative, an 8-0 decision stating that there is no exception as a Schedule I drug for people to use cannabis for medical purposes.[11] This creates an interesting tension between state and federal laws.[12]

Some local and state governments have either partially decriminalized the possession of small amounts of cannabis, or simply advised local authorities to limit enforcement of controlled substance laws to more serious offenses. A 2005 initiative ordinance in Denver, Colorado, for instance, repealed municipal penalties for possession of less than one ounce of cannabis by adults twenty-one and older, though Colorado state and federal penalties remain in effect.[13] A 2006 advisory policy adopted by the city of West Hollywood, California holds that the city's contracted law enforcement agency, the Los Angeles County Sheriff, should not target simple possession or private consumption of cannabis by adults within the city.[14][15] With the 1975 Ravin v. State decision, the Alaska Supreme Court declared the state's anti-drug law unconstitutional with respect to possession of small amounts of cannabis, holding that the right to privacy guaranteed by the Alaska state constitution outweighed the state's interest in banning the drug.[16] Despite a 1990 initiative statute and a 2006 legislative statute contradicting the Ravin decision, Alaska courts continue to follow Ravin, voiding laws which criminalize possession of small amounts of cannabis.[17][18][19]

In the November 7, 2006 election, voters in Colorado, Nevada and South Dakota rejected propositions that would have legalized possession of up to one ounce of marijuana.[20]

A 1998 study by pro-legalization lobby NORML estimated cannabis to be the largest cash crop in several non-Midwestern states, and the fourth largest cash crop nationwide.[21]

New breeding and cultivation techniques

Advances in breeding and cultivation techniques have increased the diversity and potency of cannabis strains since 1970, and these strains are now widely smoked all over the world. These advances are known as the sinsemilla techniques of production; sinsemilla, Spanish for without seed, are the dried, seedless female flowers of cannabis plants which have been grown in the absence of males to ensure no pollination takes place. Because THC potency and production drops off once pollination takes place, various techniques such as seed banks, hydroponics, cloning, lighting techniques, and the sea of green method have been utilized, in part as a response to prohibition enforcement efforts which have made outdoor cultivation more risky; thus, efficient indoor cultivation has become more common. These same advances have led to fewer seeds being present in cannabis currently than were present 20 years ago.

Many opponents of cannabis use, both in and out of government, have exaggerated the increases in potency and ramifications thereof. In the United States, government advertisements encourage parents to disregard their own experience with cannabis when speaking to their children, on the premise that pot today is significantly stronger and thus more dangerous than that which they themselves might have smoked in the past.[22] In a

general pattern of proposing reverses in cannabis rescheduling, the UK government is considering scheduling stronger cannabis (skunk, in local parlance) as a separate, more restricted substance. Many cannabis proponents disagree vehemently, reasoning that as one must smoke less cannabis to achieve the same effect, it actually is safer and less potentially carcinogenic in the long run than that which was smoked in earlier times.

Preparations for human consumption

Cannabis is prepared for human consumption in several forms:

- Marijuana or buds, the resin gland-rich flowering tops of female plants.
- Hashish, a concentrated resin mostly comprised of trichomes that are extracted physically, as with ice hash, or chemically.
- Sinsemilla or sensemillia, flowering tops which are free of seeds as a result of being grown in a pollen-free environment. Since no plant energy can go into seed formation, this version is higher in psychoactive components.
- Kief or kif, a powder containing the resin glands (glandular trichomes, often incorrectly called "crystals" or "pollen"); it is produced by sifting marijuana and leaves.
- Charas, hand-made hashish produced by hand-rubbing the resin from the resin gland-rich parts of the plant. Often thin dark rectangular pieces.
- Bhang, prepared by the wet grinding of the leaves of the plant and used as a drink.
- Hash oil, resulting from extraction or distillation of THC-rich parts of the plant with isopropyl or butane.
- Budder, processed hash oil. Ordinary hash oil is whipped to incorporate air, making it a foam. It has been marketed as being anywhere between 82% and 100% THC, though no actual lab tests have been done to validate this claim.
- Resin, when smoked through a pipe all of the above will cause black goo to create a film on the sides or collect in certain nooks depending on its shape. This can be collected and resmoked. This method is commonly referred to as scraping.
- Minimally potent leaves and detritus, called shake, brush, bush or leaf.

These forms are certainly not exclusive and combinations of two or more different forms of cannabis are common. Mixing different forms is done mainly to obtain a different or more powerful effect. Between the many different strains of Cannabis and the various ways that it is prepared for consumption, there are innumerable types of blends or mixes, similar to the countless varieties of mixed alcoholic beverages that are available.

There are two recognized subspecies of Cannabis sativa, Cannabis sativa subsp. sativa and C. sativa subsp. indica. [23]

Smoking

There are a wide variety of methods of smoking cannabis. The most popular include the joint, the blunt, the bong, the pipe more commonly called a "bowl" or "piece", the shotgun,

and the one-hitter. These are sometimes smoked inside a small closed area (such as a car) used to trap smoke so that it is inhaled with every breath. This is often referred to as "hotboxing", "fishbowling", "clam-baking", or "green-housing.". Smoking in a small enclosed area such as a car or under a blanket is commonly referred to in Australia as smoking in a "Dutch Oven".

To create a joint, cannabis is rolled up into a cigarette, using rolling paper (where available). Brown paper, newsprint, and other assorted paper products can be used, but these often contain harmful chemicals. Cannabis cigars, or blunts, can also be created by using the wrapper of a standard cigar.

A bong is a water pipe through which cannabis smoke is filtered. Variants include the gravity bong, which consists of a cone atop a perforated or cut water bottle. This method of cannabis smoking is one of the most efficient, as the presence of a chamber and carburetor reduce smoke waste.

Pipes are usually made of blown glass, wood, or non-reactive metals. Metal pipes are often made of interchangeable pieces. Glass pipes often have a carburetor, colloquially referred to as a carb, rush, choke, or shotgun, that is covered for suction then released for inhalation. Some users also prefer vertically held pipes, or improvised pipes ("tinnies") made from aluminium foil (either constructed entirely from the foil or by using it as a gauze), small plumbing fittings, soda cans, crisp fruits or vegetables, or the cardboard from bathroom-tissue or aluminium foil rolls.

A "one-hitter" is a device that allows smaller amounts of cannabis to be smoked with equal suction. Cannabis buds are loaded into a compartment for combustion. The smoker then lights the compartment and the entire amount of cannabis is smoked. This is repeated for each hit. This method is also efficient in titrating the exact dose desired.

Oral consumption

Cannabis may be orally consumed. In order to release its psychoactive properties hashish can be eaten raw or mixed with water but marijuana will only be absorbed into the bloodstream by blending it with ethanol or lipids. The effects of the drug take longer to begin, but last longer and may be perceived as more physical rather than mental, though there are claims to the contrary. A dose of oral cannabis is often considered to give a stronger experience than the equivalent dose of smoked cannabis. A common belief holds that smoking cannabis leads to a large amount of the active compounds being lost in the exhaled smoke or simply decomposing on burning, whereas ingested cannabis results in 100% consumption of the active compounds, an assertion which cannot be confirmed without objective analysis. It is thought that the active component of cannabis, ”9-THC, is converted to the more psychoactive 11-hydroxy-THC in the liver.[24] Titration is much more complex than through inhalation. Common preparations involve blending with butter, to create Cannabutter that is used in preparing Brownies, fudge, cookies, ganja goo balls or space cakes. When blended with melted butter, the drug is finely minced almost into powder form. However there are some preparations that do not contain butter in them and therefore fall into a slightly different category; these include the Leary biscuit, which requires less preparation than more "conventional" recipes. Infusion in drinks containing milk and

flavoring herbs is also possible, and more common in India. Hollowed-out gumballs filled with the drug, wrapped and distributed labeled as Greenades, were identified in 2006 as being used by high school students in the United States.[25]

As with other drugs that are taken orally, it is sometimes customary to fast before taking the drug to increase the effect, possibly because an empty stomach will absorb the drug faster so it 'hits' stronger. However, some people do eat before consuming the drug because eating it on an empty stomach makes them feel sick. Still, time to effect onset is an hour or sometimes more, as opposed to smoking, where effects can be almost immediate.

Cannabis can also be leached in high-percentage ethanol (often grain alcohol) to create Green Dragon. This process is often used to utilize otherwise low-quality stems and leaves.

Cannabis can also be consumed as a tea. THC is lipophilic and only slightly water soluble, with a solubility of only 2.8 grams per litre,[26] but enough to make a tea effective. Water-based infusion is generally considered to be inefficient.

The seeds of the plant, high in protein and fatty acids, are appreciated by many species of birds. Many countries, including the United States, make the possession of viable cannabis seeds illegal[27], although they can be openly bought and sold legally in much of Europe, including the UK.

Vaporization

With a vaporizer, cannabis can be heated to a temperature of about 365 °F (185 °C), at which the active ingredients are released into gaseous form with little or no burning of the plant material. With this method, the user does not inhale as many (or any) toxic chemicals depending on the quality of the vaporizer. Scientific studies by MAPS/NORML have yielded varied results on the effectiveness of vaporizing as a method of cannabis consumption. One particular study by MAPS/NORML found 95% THC and no toxins delivered in the vapor.[28] However, an older study by MAPS/NORML showed minimal reduction of toxins.[29]

Hot-knifing (Blades)

Hot-knifing, spots, blasting or doing blades is a process in which the tips of two knives are heated to a very high temperature, often by inserting them into the heating element of an electric or gas stove. The cannabis is then pressed between the heated knife-tips, rapidly combusting, or vaporising it depending upon the amount of heat used. The vaporized cannabis is funneled into the mouth of the smoker through the use of a glass or plastic bottle, empty pen, or other hollow tube or funnel or free handed.

In New Zealand and Australia, this is known as "spots". "Spots" can refer to both the activity of hot-kniving (aka "spotting") and the small, rolled balls of cannabis consumed in the process. Spots are much more efficient than bongs or joints; as the amount of cannabis required to constitute a hit is less and the dosage is easily controlled. This method is most commonly employed with high quality cannabis or hashish.

Another method of "spotting" uses knife blades heated to a much lower temperature, only hot enough to vaporise the active ingredients, leaving the organic material scorched, rather than burnt to ash, thus decreasing potential harmful consequences of the smoke itself.

Immediate effects of consumption

The nature and intensity of the immediate effects of cannabis consumption vary according to the dose, the species or hybridization of the source plant, the method of consumption, the user's mental and physical characteristics (such as possible tolerance), and the environment of consumption. This is sometimes referred to as set and setting. Smoking the same cannabis either in a different frame of mind (set) or in a different location (setting) can alter the effects or perception of the effects by the individual. Effects of cannabis consumption may be loosely classified as cognitive and physical. Anecdotal evidence suggests that drug varieties of Cannabis sativa subsp. sativa tend to produce more of the cognitive or perceptual effects, while C. sativa subsp. indica tends to produce more of the physical effects.

Active ingredients, metabolism, and method of activity

Of the approximately 315[30] different psychoactive chemicals found in Cannabis, the main active ingredient is tetrahydrocannabinol (delta-9-tetrahydrocannabinol, *THC*). THC can degrade to other cannabinoids, such as cannabidiol or cannabinol, which can make one feel sleepy and disoriented. Different cannabis products have different ratios of these and other cannabinoids. Depending on the ratio, the quality and nature of the "high" will vary.

THC has an effect on the modulation of the immune system, which may have an effect on malignant cells, but there is insufficient scientific study to determine whether this might promote or limit cancer. Cannabinoid receptors are also present in the human reproductive system, but there is insufficient scientific study to conclusively determine the effects of cannabis on reproduction. Mild allergies to cannabis may be possible in some members of the population.

A study has shown that holding cannabis smoke in one's lungs for longer periods of time does not conclusively increase THC's effects on psychological test performance.[31] However, a more recent study by the same authors indicates that a longer breath-holding duration increases the subjective ratings of ones' "high."[32] This latter study also found that a long breath-holding duration decreased subjects' subjective ratings of "calmness" more than a short breath-holding duration. Additionally, subjects who held cannabis smoke in their lungs for a long duration felt slightly less "relaxation" while subjects who held the smoke for a short period gave higher "relaxation" ratings.

List of effects

Cannabis has a broad spectrum of possible cognitive, behavioral, and physiological effects, the occurrence of which vary from user to user. Some of these are the intended effect desired by users, some may be considered desirable depending on the situation, and others are generally considered undesirable. Users of cannabis report that these kinds of effects are more often produced by material derived from Cannabis sativa subsp. sativa.

Cannabis also has effects that are predominantly physical or sensory, widely believed to be more common with material derived from C. sativa subsp. indica.

Cognitive effects

- Short or long-term psychosis/schizophrenic disorders that begin in some young users [33]
- Varying amounts of paranoia and anxiety in some users (usually when overdosed or anxious before use)[34]
- Some studies report the loss of coordination and distorted sense of time in some users[35], while others fail to find effects on time perception and reaction time. [36]
- Impairment of short-term memory in some heavy users (7 cigarettes a week and more) [37]

- Auditory or visual hallucinations at high doses in some users[38]
- Increased mental activity, like metacognition and introspective or meditative states of mind in most users[39]
- Relaxation or stress reduction in some users
- Entheogenesis (e.g. per Rastafarian users, more "Jah-Vibrations") in some users[40]

Additionally, cannabis affects blood flow to the brain by narrowing blood vessels analogous to how heart disease affects blood flow. Although studies have not proven altogether conclusive on the subject, recent work suggests that blood flow of those consuming less than 70 joints a week shows improvement after a month's cessation.[41]

Behavioral effects

- Varying degrees of euphoria (though usually mild) and feelings of well-being[42]

Physiological effects

- Antiemetic properties (in moderate doses) [43]
- Lowered intraocular pressure, beneficial to glaucoma patients and sufferers of certain types of headaches, cramps, and eye pain.
- Dilation of blood vessels (vasodilatation),[44] resulting in:
    - Increased blood flow and heart rate (possibly even tachycardia)
    - Reddening or drying of eyes
- Lower blood pressure while standing. Higher blood pressure while sitting (note that this can lead to instances of orthostatic hypotension, also known as head rush).[45]
- Change in appetite, increase (often referred to as "the munchies") is an effect of stimulation of the endocannabinoid system, which affects body weight, insulin resistance, and dyslipidemia[46] though recent scientific and ongoing anecdotal evidence also points to it as an appetite suppressant.
- Varying degrees of dry (cotton) mouth[47]
- Dilation of alveoli (air sacs) in lungs, resulting in deeper respiration and increased coughing.

Lethal dose

According to the Merck Index, 12th edition, the LD50, the lethal dose for 50% of rats tested by inhalation, is 42 mg/kg of body weight. That is the equivalent of a 165 lb (75 kg) man ingesting all of the THC in 21 one-gram cigarettes of high-potency (15% THC) cannabis buds at once, assuming no THC was lost through burning or exhalation. For oral consumption, the LD***50*** for rats is 1270 mg/kg and 730 mg/kg for males and females,

respectively, equivalent to the THC in about a pound of 15% THC cannabis. Only with intravenous administration may such a level be even theoretically possible. [48] The ratio of cannabis required to saturate cannaboid receptors to the amount of cannabis required to have a fatal over dose is 1:40,000.

There has only ever been one recorded instance of an alleged fatal overdose due to cannabis. In January 2004, Lee Maisey of Pembrokeshire, Wales was found dead. The coroner's report stated "Death due to probable cannabis toxicity". It had been reported that Maisey smoked about six joints a day. Mr. Maisey's blood contained 130 nanograms per milliliter (ng/ml) of the THC metabolite THC-COOH. However, the validity of the finding did not stand up well under review. As reported on 2004-01-28 in the Neue Züricher Zeitung, the Federal Health Ministry of Switzerland asked Dr. Rudolf Brenneisen, a professor at the department for clinical research at the University of Bern, to review the data of this case. Dr. Brenneisen said that the data of the toxicological analysis and collected by autopsy were "scanty and not conclusive" and that the conclusion "death by cannabis intoxication" was "not legitimate."[49]

Health issues and the effects of cannabis

There is some conclusive scientific evidence about the long-term effects of human cannabis consumption.[50]

The most significant confounding factor is the use of other drugs, including alcohol and tobacco, by test subjects in conjunction with cannabis. When subjects using only cannabis were combined in the same sample with subjects using other drugs as well, researchers could not reach a conclusion as to whether their findings were caused by cannabis, other drugs, or the interaction between them. In addition, research using cannabis is heavily restricted in many countries, making it difficult to get new studies funded or approved. Since there are so many different compounds in cannabis, it is difficult to predict or accurately measure its effects. Some conclusions established with some degree of certainty that cannabis is less likely to cause emphysema or cancer than tobacco[51]; that it is unlikely to cause birth defects or developmental delays in the children of users,[52][53] and in a study done by the University of California Los Angeles in 2006, that even heavy cannabis smokers do not increase their risk for lung cancer.[54] According to a United Kingdom government report, using cannabis is less dangerous than both tobacco and alcohol in social harms, physical harm and addiction.[55]

Newer research has also shown that cannabis use is generally higher among sufferers of schizophrenia, but causality has not been established[56][57] and confirmed that sustained early-adolescent cannabis use among certain genetically predisposed individuals has an elevated correlation with certain mental illness outcomes, ranging from psychotic episodes to clinical schizophrenia.[58][59]

Legality

Since the 20th century, most countries have enacted laws against the cultivation, use, possession, or transfer of cannabis for recreational use. Naturally, these laws impact adversely on the cannabis plant's cultivation for non-recreational purposes, but there are

many regions where, under certain circumstances, handling of cannabis is legal or licensed, and others where laws against its use, possession, or sale are not enforced. Many jurisdictions have also decriminalized possession of small quantities of cannabis, so that it is punished by confiscation or a fine, rather than imprisonment. By effectively removing the user from the criminal justice system, decriminalization focuses more on those who traffic and sell the drug on the black market. However, this does not solve the problem of how a user will obtain the "legal amount" of cannabis, since buying or growing cannabis is still illegal. Increasingly, many jurisdictions also permit cannabis use for medicinal purposes. Some countries allow the sale through drug companies. However, simple possession can carry long jail sentences in some countries, particularly in East Asia, where the sale of cannabis may lead to a sentence of life in prison or even execution.

Recent history

Under the name cannabis, 19th century medical practitioners sold the drug, (usually as a tincture) popularizing the word amongst English-speakers. It was rumoured to have been used to treat Queen Victoria's menstrual pains as her personal physician, Sir John Russell Reynolds, was a staunch supporter of the benefits of cannabis.[60] Cannabis was also openly available from shops in the US. By the end of the 19th century, its medicinal use began to fall as other drugs like aspirin took over its use as a pain reliever.

In 1894, the Report of the Indian Hemp Drugs Commission commissioned by the UK Secretary of State and the government of India, was instrumental in the decision not to criminalize the drug in those countries. The Report, which at over 500 pages remains one of the most complete collections of information on cannabis in existence, shows the stark contrast in the way that the American and British governments went about deciding whether to criminalize cannabis.[61]

The name marijuana (Mexican Spanish marihuana, mariguana) is associated almost exclusively with the plant's psychoactive use. The term is now well known in English largely due to the efforts of American drug prohibitionists during the 1920s and 1930s, which deliberately used a Mexican name for cannabis in order to turn the populace against the idea that it should be legal.

Although cannabis has been used for its psychoactive effects since ancient times, it first became well known in the United States during the jazz music scene of the late 1920s and 1930s. Louis Armstrong became a prominent and life-long devotee. It was popular in the blues scene as well, and eventually became a prominent part of 1960s counterculture.

Decriminalization and legalization

In recent decades, a movement to decriminalize cannabis has arisen in several countries . This movement seeks to make simple possession of cannabis punishable by only confiscation or a fine, rather than prison. In the past several years, the movement has started to have some successes. These include Denver, Colorado legalizing possession of up to an ounce of cannabis[62], a broad coalition of political parties in Amsterdam, Netherlands unveiling a pilot program to allow farmers to legally grow it,[63] and Massachusetts voting

in favor of a bill to decriminalize the possession of up to an ounce of cannabis[64]. Also, in Alaska, cannabis was decided legal for in-home, personal use under the Raven vs. State ruling in 1975. This ruling allowed up to four ounces of cannabis for these purposes. In a response to former Governor Frank Murkowski's successive attempt to re-criminalize cannabis, the ACLU filed a lawsuit against the state and on July 17, 2006, Superior Court Judge Patricia Collins awarded the Case Summary judgement to the ACLU. However she said, "No specific argument has been advanced in this case that possession of more than 1 ounce of cannabis, even within the privacy of the home, is constitutionally protected conduct under Ravin or that any plaintiff or ACLU of Alaska member actually possesses more than 1 ounce of cannabis in their homes.", at first glance it appears that possession has been reduced to one ounce when in fact this was a mere case summary review filed by the ACLU, and she even said "A lower court cannot reverse the State Supreme Court's 1975 decision in Ravin v. State" and "Unless and until the Supreme Court directs otherwise, Ravin is the law in this state and this court is duty bound to follow that law". The law regarding possession of cannabis has not changed in Alaska, and the Supreme Court has rejected to review the case, therefore the law still stands at 4 ounces.[citation needed] In 2001 in the United Kingdom, it was announced that cannabis would become a Class C drug, rather than a Class B, this change took effect in 2004. Since then there has recently been some controversy amongst UK politicians about the message this sends out, with some calling for its reclassification to Class B. [65] The Government of Mexico voted to legalize the possession of cannabis under 5 grams on April 28, 2006. [66] However, as of May 3, 2006, Mexican President Vicente Fox has said that he will not sign this proposed law until Congress removes the parts that would decriminalize the possession of small quantities of drugs[67] and vetoed the bill on May 4, 2006,[68] sparking broad controversy over the bill.[69][70][71] In the early summer of 2006 Fox and the Mexican congress came to an agreement and legalized possession of small amounts (and also measured amounts of other drugs). On July 17th, 2006, Italian Social Solidarity Minister Paolo Ferrero, speaking of the urgent need for depenalising the consumption of light drugs, said that "a joint is less harmful than a litre of wine." [72] In The Australian state of South Australia and the Australian Capital Territory, two plants both less than 6 ft tall are allowed for personal use.

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Dissociatives

A *dissociative* is a drug which reduces (or blocks) signals to the conscious mind from other parts of the brain, typically, but not necessarily, limited to the physical senses. Such a state of sensory deprivation and dissociation can facilitate self exploration, hallucinations, and dreamlike states of mind which may resemble some psychedelic mindstates. Essentially similar states of mind can be reached via contrasting paths—psychedelic or dissociative. That said, the entire experience, risks and benefits are markedly different.

The primary dissociatives are similar in action to phencyclidine (PCP), and include ketamine and dextromethorphan. Also included are nitrous oxide (laughing gas), salvia divinorum, and muscimol from the amanita muscaria (fly agaric) mushroom.

Many dissociatives also have central nervous system depressant effects, thereby carrying similar risks as opioids to slowing breathing or heart rate to levels resulting in death, when using very high doses.

Their effects are characterized by intense feelings of depersonalization, derealization, and analgesia.

Pharmacological classes of dissociatives, and their general subjective effects

Entries marked with a # are naturally occurring.

NMDA receptor antagonists and sigma1 ligands

- dextromethorphan
- ketamine
    - memantine
- phencyclidine, *PCP*
    - Ibogaine # (is also classed as a psychedelic)
    - dizocilpine

riluzole
Tiletamine
MK-801 (dizocilpine)

Kappa opioid receptor agonists

- Salvinorin-A #, the active constituent of Salvia divinorum (diviner's sage)
Enadoline
ibogaine (Weak / Complex mechanism of action)
Pentazocine

Inhalants

- Nitrous oxide

Amanita muscaria constituents

- Muscimol # GABA-A agonist, primary active constituent
Ibotenic acid # NMDA agonist, metabolizes to muscimol
- Muscarine # muscarinic ACh agonist, trace constituent, deliriant

These four groups of dissociatives have slightly different effects but also share similarities separating them from other classes of hallucinogens. They are markedly different from psychedelics such as LSD, where alert and fully conscious users experience cognitive distortion while simultaneously interacting with the "real world". Hallucinations from these dissociatives are generally only experienced in dark rooms or with eyes closed, unless at very high doses above what is normally consumed recreationally. Nitrous oxide has very different effects however, and even at low doses includes auditory distortions. Unlike with many other psychedelic chemicals, salvia users are generally not ambulatory and the experience is frequently dissociative. Often a very brief trance is entered, where the user experiences an intense and very realistic dream state. On the other hand, the effect of salvia on emotion has been reported to be less marked than that of true psychedelics.

Although muscimol does not usually cause normal hallucinations, it has a tendency to put the user to sleep, during which the user is able to have very vivid dreams with good dream recall.

See also

- Deliriant
- Psychedelic drug
- Psychoactive drug

Hypnotics

Hypnotic drugs are a class of drugs that induce sleep (which differentiates them from the sedative category), used in the treatment of severe insomnia and in surgical anesthesia. Often the treatment of insomnia will not begin with drugs at all, however, as many (not all) hypnotic drugs are habit forming. A physician will usually recommend alternative sleeping patterns and exercise before prescribing medication for sleep. This is due to a large number of factors known to disturb the human sleep pattern.

These drugs include barbiturates, benzodiazepines, zolpidem, zaleplon, zopiclone, eszopiclone, chloral hydrate, chlormethiazole or the antihistamines doxylamine, promethazine, and diphenhydramine. Alcohol is often tried as a hypnotic drug but it is not particularly effective.

Mood stabilizers

A *mood stabilizer* is a psychiatric medication used to treat mood disorders characterized by rapid and unstable mood shifts. These disorders include bipolar disorder, where mood stablizers suppress swings between mania and depression, and borderline personality disorder. Most mood stabilizers are anticonvulsants, with the important exception of lithium.

Mood stabilizers include:

- Lithium carbonate — the first Food and Drug Administration-approved mood stabilizer, and still popular in treatment. Therapeutic drug monitoring required. Monitor blood lithium levels (therapeutic range: 0.6 or 0.8-1.2 mEq/L) and look for signs and symptoms of toxicity (such as nausea, vomiting, diarrhea, ataxia).
- Valproic acid (Depakene®), divalproex sodium (Depakote®), and sodium valproate (Depacon®) — Available in extended release form. Can be very irritating to the stomach, especially when taken as valproic acid. Liver function and CBC should be monitored. Therapeutic drug monitoring is required. Lamotrigine (Lamictal®) — Particularly effective for bipolar depression. Monitor for signs and symptoms of Stevens-Johnson syndrome, very rare but can be fatal.
- Carbamazepine (Tegretol®) — CBC should be monitored; can lower white blood cell count. Therapeutic drug monitoring is required. Not FDA-approved for bipolar disorder, but widely used for many years.
- Gabapentin (Neurontin®) — Not FDA approved for bipolar disorder. Recent scientific studies suggest it is not an effective treatment, however many psychiatrists continue to use it.
- Oxcarbazepine (Trileptal®) — Not FDA approved for bipolar disorder.
- Topiramate (Topamax®) — Not FDA approved for bipolar disorder.

Sometimes mood stabilizers are used in combination, such as lithium with one of the anticonvulsants.

Many atypical antipsychotics also have mood stabilizing effects and are thus commonly prescribed even when psychotic symptoms are absent. It is also conjectured that Omega-3 fatty acids may have a mood stabilizing effect. However, more research is needed to verify this (a multi-year study of this is now being carried out as of 2001).

Most mood stabilizers are effective at treating mania and mood cycling and shifting, but are not very effective at treating depression (with lamotrigine and lithium carbonate being exceptions). Often, an antidepressant is prescribed in addition to the mood stabilizer during depressive phases. However this brings some risks, as antidepressants can induce mania, psychosis, and other disturbing problems in bipolar patients, particularly when taken alone, but sometimes even when used with a mood stabilizer.

References

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Phenethylamines

Phenethylamine

Chemical name 2-Phenylethylamine

Other names Phenethylamine, ²-Phenylethylamine, 2-Phenyl-1-aminoethane, ²-Aminoethylamine, 2-Phenylethanamine

Chemical formula $C_8H_{11}N$

Molecular mass 121.18 g/mol

CAS number [64-04-0]

Density 0.964 g/cm^3

Melting point -60 °C

Boiling point 194.5-195 °C

SMILES c1ccccc1CCN

Phenethylamine, or ²-Phenylethylamine, is an alkaloid and monoamine. In the human brain, it is believed to function as a neuromodulator or neurotransmitter (trace amine). Phenethylamine is a natural compound biosynthesized from the amino acid phenylalanine

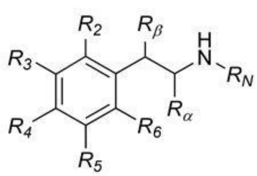
by enzymatic decarboxylation. It is also found in many foods such as chocolate, especially after microbial fermentation. It has been suggested that phenethylamine from food may have psychoactive effects in sufficient quantities. However, it is quickly metabolized by the enzyme MAO-B, preventing significant concentrations from reaching the brain.

Substituted phenethylamines are a broad and diverse class of compounds that include neurotransmitters, hormones, stimulants, hallucinogens, entactogens, anorectics, bronchodilators, and antidepressants. The phenethylamine structure can also be found as part of more complex ring systems such as the ergoline system of LSD or the morphinan system of morphine.

Chemistry

Phenethylamine is an aromatic amine which is a colorless liquid at room temperature. It is soluble in water, ethanol, and ether.[1] Similar to other low molecular weight amines, it has a fishy odor. Upon exposure to air, it forms a solid carbonate salt with carbon dioxide. Phenethylamine is strongly basic and forms a stable crystalline hydrochloride salt with a melting point of 217 °C. Phenethylamine is also a skin irritant and possible sensitizer.

Substituted phenethylamines



General structure of phenethylamines and amphetamines (see the table below).

Substituted phenethylamines carry additional chemical modifications at the phenyl ring, the sidechain, or the amino group:

- Amphetamine are homologues of phenethylamines carrying an alpha-methyl (±-CH3) group at the sidechain carbon atom next to the amino group.
- Catecholamines are phenethylamines carrying two hydroxy groups in positions 3 and 4 of the phenyl ring. Examples are the hormones and neurotransmitters dopamine,
- The aromatic amino acids phenylalanine and tyrosine are phenethylamines carrying a carboxyl group (COOH) in alpha position.

Pharmacology

Many substituted phenethylamines are pharmacologically active drugs due to their similarity to the monoamine neurotransmitters:

- Stimulants like the plant alkaloids Ephedrine and cathinone and the synthetic drugs Amphetamine (speed, benzedrine) and methylphenidate
- Hallucinogens like the plant alkaloid mescaline and the synthetic drug 2C-B

- Empathogen-entactogens **like** MDMA **(*ecstasy*) and MDA**
    - Anorectics like phentermine, fenfluramine, and Amphetamine
- Bronchodilators **like** salbutamol **and Ephedrine**
- Antidepressants **like** bupropion **and the** monoamine oxidase inhibitors **phenelzine and tranylcypromine.**

References

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2C-T-7

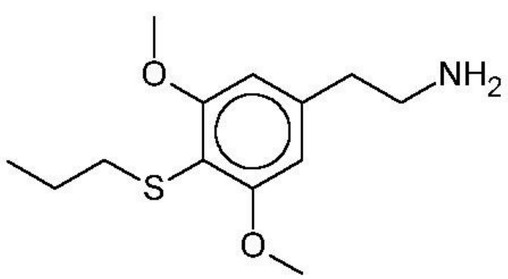
Chemical name 2-[2,5-dimethoxy-4-(propylthio)phenyl]ethanamine

Chemical formula C***13***H***21***NO***2***S

Molecular mass 255.3799

CAS numbers 207740-26-9

SMILES COc1cc(SCCC)c(cc1CCN)OC



THIS IS ACTUALLY 3,5 dimethoxy, NOT 2,5 dimethoxy. SOMEONE PLEASE CORRECT IT.

2C-T-7 is a psychedelic phenethylamine and is sometimes used as an entheogen. It was presumably first synthesized in 1986 by Alexander Shulgin. It has structural and pharmacodynamic properties similar to the drugs Mescaline, MDMA, 2C-T-2 and 4-MTA. An often used slang term for 2C-T-7 is "watusi".

Chemistry

2C-T-7 is 4-(n)-propylthio-2,5-dimethoxyphenethylamine with the formula C12H21O2NS. The full name of the chemical is 2-[2,5-dimethoxy-4-(propylthio)phenyl]ethanamine.

Pharmacology

2C-T-7 is a hallucinogenic phenethylamine. In his book PIHKAL (Phenethylamines I Have Known and Loved), Shulgin lists the dosage range as 10-30mg. 2C-T-7 is generally taken orally, and produces psychedelic and entheogenic effects that last 8 to 12 hours.

The mechanism that produces the hallucinogenic and entheogenic effects of 2C-T-7 is most likely to result from action as a 5-HT2A serotonin receptor agonist in the brain, a mechanism of action shared by all of the hallucinogenic tryptamines and phenethylamines.[1]

2C-T-7 also has a separate action as a selective monoamine oxidase A inhibitor. This makes 2C-T-7 a potentially dangerous drug as at high doses it can slow down the degradation of serotonin in the brain, which can lead to serotonin syndrome and potential death without treatment.[2]

Several of the deaths involving 2C-T-7 followed co-administration of the drug with other stimulants such as MDMA and Ephedrine, and so these kind of combinations should be avoided.

Recreational usage

2C-T-7 has been sold on the street under the names "Blue Mystic," "Tweetybird Mescaline," "7th Heaven," and "Lucky 7." The drug can be taken orally or snorted, and can be lethal even in small doses.[3]

Around the year 2000, 2C-T-7 began to change from an obscure chemical to a drug used at parties and clubs in North America and Europe as it became available through a number of grey-market commercial vendors.

There have been at least three reported deaths related 2C-T-7 use, and in January of 2002, Rolling Stone published an article about 2C-T-7 entitled "The New (legal) Killer Drug". It can cause nausea and may be dangerous when combined with alcohol.

Legality

On September 20, 2002, 2C-T-7 was classified as a Schedule I substance in the United States by an emergency ruling by the DEA.

References

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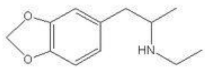
MDEA

 MDEA

MDEA (also *MDE*), which stands for 3,4-methylenedioxy-N-ethylamphetamine, is a psychedelic hallucinogenic drug and empathogen-entactogen of the phenethylamine family. It is chemically very similar to MDMA, the active chemical in the drug "ecstasy". MDEA differs from MDMA in that it has one more carbon atom, and two more hydrogen atoms in the substituent on the nitrogen atom. The difference is evidenced in its name by the "ethyl" prefix, rather than the "methyl" prefix designating a single-carbon chain (see Alkanes). MDEA is sometimes sold as a substitute for ecstasy on the black market. It can be prepared by reductive amination of MDP2P.

MDEA works by releasing serotonin, a neurotransmitter that affects mood and perception. It requires a slightly larger dose (100 - 200 mg.) than MDMA with major effects lasting typically between 3 and 5 hours [1]. The subjective effects of MDEA are similar to MDMA. The euphoric 'loved up' feelings associated with MDMA use are not as pronounced. The effects are also not as stimulating as MDMA, MDE has somewhat of a stoning effect and may be responsible for rumors of heroin-laced ecstasy pills. However, MDEA does have a mildly hallucinogenic effect. This, coupled with an increase in the user's energy levels (similar to amphetamine use) had led some users to conclude that MDEA is more suitable as a nightclub drug.

Mescaline

Chemical name 3,4,5-Trimethoxy- phenethylamine or 2-(3,4,5-trimethoxyphenyl) ethanamine

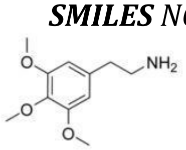
Chemical formula C***11***H***17***NO***3***

Molecular mass 211.26 g/mol

Melting point 128–129 °C

CAS numbers 54-04-6

SMILES *NCCC1=CC(OC)=C(OC)C(OC)=C1*



Mescaline (3,4,5-trimethoxyphenethylamine) is a hallucinogenic alkaloid of the phenethylamine class.

It occurs naturally in the peyote cactus (Lophophora williamsii), the San Pedro cactus (Echinopsis pachanoi), in the Peruvian Torch cactus (Echinopsis peruviana), and it is also found in a number of other members of the Cactaceae. It can be extracted from these sources. Mescaline was first isolated and identified in 1897 by the German Arthur Heffter and first synthesized in 1919 by Ernst Späth.

Usage and history

The use of extract from peyote in Native American religious ceremonies has been noted since the earliest European contact, notably by the Huichols in Mexico.

Dosage and effects

For the drug to take effect, disk-shaped buttons are cut from the roots, on the top of the cactus, and dried. It is chewed to produce its effect or soaked in water for an intoxicating drink. The effective human dosage is 0.3–0.5 grams, with the effects lasting for up to 12 hours. Users typically experience visual hallucinations and radically altered states of consciousness, often experienced as pleasurable and illuminating but occasionally as accompanied by feelings of anxiety or revulsion. It is not physically addictive.

Legal status

In the US it was made illegal in 1970 by the Comprehensive Drug Abuse Prevention and Control Act. It was prohibited internationally by the 1971 Convention on Psychotropic Substances[1] and is categorised as a Schedule I hallucinogen by the CSA.

Chemistry

A common synthetical approach starts from 3,4,5-trimethoxybenzaldehyde (PiHKAL entry).

Side effects

One or more of the following side effects may or may not accompany any individual experience with mescaline.

- Open eye visuals

Closed-eye visuals
New thought processes
Dream-like scenarios
Euphoria
Mystical experience
Pupil dilation

Sensations of warm and cold
Temporary splitting/destruction of ego
Dizziness
Vomiting
Tachycardia
Diarrhea
Headaches
Anxiety
Feeling of dying or genocide
Fear of not being able to return to normal consciousness
Hallucinogen persisting perception disorder (HPPD)
Irrationality of the thought-process

Famous users

- Jerry Garcia

Aldous Huxley
Carlos Santana
Ernst Jünger [2]
Leo Kenney [3]
Henri Michaux [4]
Jim Morrison
Carlos Castaneda
Hunter S. Thompson
Allen Ginsberg
Anton Malinsky
Robert Del Naja
Timothy Leary
Christopher Mayhew, Labour MP and BBC television personality, who took Mescaline Hydrochloride in 1955 for an unbroadcast episode of Panorama [5]
Jean-Paul Sartre
Antonin Artaud
Sébastien Branconnier
Comedian Jim Breuer, in his stage act, talks about trying it once as a teenager, in a bit called "The Wizard".
StanisBaw Ignacy Witkiewicz, Polish writer, dramatist, photographer, philosopher and painter.
Don Henley, Glenn Frey, Joe Walsh and Don Felder from The Eagles.
Helen Reddy, singer, actress, and feminist activist
Roland Deschain (AKA The Gunslinger), Although a fictional user - Roland's use of Mescaline is prevalent in the first book of the 'Dark Tower' cycle. Roland uses the drug in order to commune with a Demon in a stone circle, and protect the child Jake.
In the film, The Royal Tenenbaums, the character Eli Cash admits to using Mescaline in a nonchalant manner. At the end of the film, it is possible he used

Mescaline when he crashed his car into the Tenenbaums' house.
In the film Domino (featuring Keira Knightley, Lucy Liu & Mickey Rourke), the bounty hunters have their coffee spiked with Mescaline as they attempt their escape.
In the novel Fear and Loathing in Las Vegas and its film adaptation, Raoul Duke uses Mescaline.
In the film The Matrix, one of Neo's friends Choi says that he uses Mescaline as it is "the only way to fly". But Yeshwanth disagrees to that statement.

See also

- Phenethylamines
- Psilocybin
- Peyote
- Psychedelic drug
- Psychoactive drug

Methylphenidate

Systematic (IUPAC) name

methyl 2-phenyl-2-(2-piperidyl)acetate

Identifiers

CAS number 113-45-1

ATC code N06**BA04**

PubChem 4158

DrugBank APRD00657

Chemical data

Formula $C_{14}H_{19}NO_2$

Mol. weight 233.306 g/mol

Pharmacokinetic data

Bioavailability **11–52%**

Metabolism Liver

Half life 2–4 hours

Excretion Urine

Therapeutic considerations

Pregnancy cat. C

Legal status Class B(UK) Schedule II(US)

Indicated for:

ADD
ADHD
narcolepsy
Recreational uses:
Stimulant / "Speed" / "Uppers"
Other uses:
treatment-resistant depression
appetite suppressant

antidepressant augmentation

Contraindications:
Use of tricyclic antidepressants (e.g. desipramine), as MPH may dangerously increase their plasma concentrations, leading to potential toxic reactions (mainly, cardiovascular effects).
Use of MAO Inhibitors, such as phenelzine (Nardil) or tranylcypromine (Parnate), and certain other drugs.
MPH should not be given to patients who suffer from the following conditions: Severe Arrhythmia, Hypertension or Liver damage.
Drug-seeking behaviour
Pronounced agitation or nervousness

Side effects:

Cardiovascular:
Tachycardia
Arterial hypertension
Endocrinal:
Appetite loss
Eye:

Blurred vision
Pupil dilation (If snorted)
Gastrointestinal:
Nausea/vomiting, abdominal pain
Musculoskeletal:
Muscle twitches
Neurological:
Insomnia, drowsiness, dizziness, headache
Psychological:
Nervousness
Euphoria
Respiratory:
Increased respiration rate

Methylphenidate (*MPH*) is an Amphetamine-like prescription stimulant commonly used to treat Attention Deficit Hyperactivity Disorder (ADHD) in children and adults. It is also one of the primary drugs used to treat symptoms of traumatic brain injury and the daytime drowsiness symptoms of narcolepsy and chronic fatigue syndrome. Brand names of drugs that contain methylphenidate include *Ritalin*® (*Ritalina*®, *Rilatine*®), *Attenta*®, *Concerta*® (a timed-release capsule), *Metadate*®, *Methylin*® and *Rubifen*®. *Focalin*® is a preparation containing only dextro-methylphenidate, rather than the usual racemic dextro- and laevo-methylphenidate mixture of other formulations.

History

Methylphenidate was patented in 1954 by the Ciba pharmaceutical company (one of the predecessors of Novartis) and was initially prescribed as a treatment for depression, chronic fatigue, and narcolepsy, among other ailments. Beginning in the 1960s, it was used to treat children with ADHD, known at the time as hyperactivity or minimal brain dysfunction (MBD). Today methylphenidate is the medication most commonly prescribed to treat ADHD around the world. According to most estimates, more than 75 percent of methylphenidate prescriptions are written for children, with boys being about four times as likely to take methylphenidate than girls. Production and prescription of methylphenidate rose significantly in the 1990s, especially in the United States, as the ADHD diagnosis came to be better understood and more generally accepted within the medical and mental health communities. Methylphenidate has been used illegally by students for whom the drug has not been prescribed, to assist with coursework and examinations. [1]

While ADHD medication is directed for children, it has not been studied for children under the age of 6. It is also important to note that while ADHD is a condition that includes hyperactivity, problems holding still, and following directions, this is also typical of a child under the age of 6. This causes difficulty in diagnosing children under this age and should probably not be studied.[1]

Most brand-name Ritalin is produced in the United States, although methylphenidate is also produced in Mexico and Argentina by respective contract pharmaceutical manufacturers and is most commonly marketed under the brand name "Ritalin" for Novartis. In the United States, various generic forms of methylphenidate are also produced by several

pharmaceutical companies (such as Methylin, etc.), and Ritalin is also sold in the United Kingdom, Germany, and other European countries (although in much lower volumes than the United States). These generic versions of methylphenidate tend to outsell brand-name "Ritalin" four-to-one. In Belgium the product is sold under the name "Rilatine" for Novartis.

Another medicine is Concerta, a once-daily extended release form of methylphenidate, which was approved in April 2000. Studies have demonstrated that long-acting methylphenidate preparations such as Concerta are just as effective, if not more effective, than IR (instant release) formulas. [2] [3][4] [5] Time-release medications are also harder to misuse.

In April 2006, the FDA approved a transdermal patch for the treatment of ADHD, called Daytrana. The once-daily patch administers methylphenidate in doses of 10, 15, 20, or 30mg.[6] However, the patch must be applied several hours before the effect is desired, and the drug's effect remains for several hours after removal, making it necessary to remove the patch in the mid-to-late afternoon or else insomnia may result.

Effects

Methylphenidate is a central nervous system (CNS) stimulant. It is claimed to have a 'calming' effect on many children who have ADHD,[7] reducing impulsive behavior and the tendency to "act out", and helps them concentrate on schoolwork and other tasks. Adults who have ADHD often claim that MPH increases their ability to focus on tasks and organize their lives.

Methylphenidate has been found to have a lower incidence of side-effects compared to dextroamphetamine, a less commonly prescribed medication. [8] When prescribed at the correct dosage, methylphenidate is usually well-tolerated by patients.[2]

The means by which methylphenidate helps people with ADHD are not well understood. Some researchers have theorized that ADHD is caused by a dopamine imbalance in the brains of those affected. MPH is a dopamine reuptake inhibitor, which means that it increases the level of the dopamine neurotransmitter in the brain by partially blocking the transporters that remove it from the synapses. [9] An alternate explanation which has been explored is that the MPH affects the action of serotonin in the brain.[10]

In the United States, methylphenidate is classified as a Schedule II controlled substance, the designation used for substances that have a recognized medical value but which have a high potential for abuse because of their addictive potential. Internationally, methylphenidate is a Schedule II drug under the Convention on Psychotropic Substances. [11] Some people abuse MPH by crushing the tablets and snorting them, the "high" resulting from the increased rate of dopamine transporter blockade due to quicker absorption into the bloodstream. In this manner, the effect of Ritalin is similar to that of cocaine or Amphetamine and such abuse can lead to addiction. When taken orally in prescribed doses, MPH has a low addiction liability and rarely produces a "high".

Side effects

Common reported side effects are[12][13]: difficulty sleeping (which can lead in turn to other problems); loss of appetite (thus its use as an appetite suppressant); Depression; irritability; nervousness; stomach aches; headaches; dry mouth; blurry vision; nausea; dizziness; drowsiness; motor tics or tremors. Up to 5% of children experience disturbing hallucinations often involving worms, snakes, or insects (New Scientist, 31 March 2006).

Less common side effects are: hypersensitivity; anorexia; palpitations; blood pressure and pulse changes; cardiac arrhythmia; anemia; scalp hair loss; toxic psychosis.

There have also been reports of: abnormal liver function; cerebral arteritis; leukopenia; death. There have been at least 19 cases of sudden death in children taking methylphenidate, leading to calls by the Drug Safety and Risk Management Advisory Committee to the FDA to require the most serious type of health warning on the label, but this advice was rejected (New Scientist 18 Feb. 2006).

Medline [14] lists a number of side-effects of unquantified frequency.

Formulations

Most products containing methylphenidate contain a racemic mixture of dextro-methylphenidate and levo-methylphenidate, although it is only dextro-methylphenidate, the active enantiomer, which is considered to provide the pharmacologically useful effects of mental focus. However, with the introduction of Focalin, pure dextro-methylphenidate is available. Described as a fast-acting form of the drug, it is absorbed more quickly by the body, with a shorter time to peak concentration (and excretion) than with the racemic compound.

The pharmacological profiles and relative usefulness of dextro- and levo-methylphenidate is analogous to what is found in amphetamine, where dextro-amphetamine is considered to have a more beneficial effect than levo-amphetamine.

Delivery

Ritalin: 5 mg, 10 mg and 20 mg tablets;
Ritalin SR: 20 mg tablets;
Ritalin LA: 20 mg, 30 mg and 40 mg capsules;
Attenta: 10mg tablets;
Methylin: 5 mg, 10 mg, and 20 mg tablets;
Methylin ER: 10 mg and 20 mg tablets;
Metadate ER: 10 mg and 20 mg tablets;
Metadate CD: 10 mg, 20 mg and 30 mg capsules;
Concerta: 18 mg, 27 mg, 36 mg and 54 mg tablets;
Equasym: 5 mg, 10 mg tablets;
Rubifen: 5 mg, 10 mg and 20 mg tablets;
Daytrana: 10 mg, 15 mg, 20 mg, 30 mg and 40 mg patches

Criticism

Similarity to Cocaine

Like cocaine, methylphenidate is a powerful stimulant that increases alertness and productivity. Methylphenidate and cocaine have similar chemical structures. [15] Their effects, too, are similar; both increase the brain-levels of dopamine -- a joy-inducing neurotransmitter -- by blocking the ability of neurons to reabsorb dopamine. When taken as prescribed, however, Methylphenidate is absorbed into the body at a much slower rate than cocaine. In this way, methylphenidate is like low-dosage, slow-acting cocaine. [16] The similarities between methylphenidate and cocaine have prompted concern that the unknown dangers of methylphenidate could be similar to the known dangers of cocaine. [17] There have also been some reports showing a cross-tolerance between cocaine, methylphenidate, and a third common stimulant, amphetamine. [18]

Overprescription

The incidence of ADHD is believed to be between three and five percent of the population, while the number of children in America taking Ritalin is estimated at one to two percent. [19] In a small study of four American communities, the incidence of ADHD varied from 1.6% to 9.4%. The study also found that 12.5% of the children meeting the DSM-III-RADHD criteria for ADHD had been treated with stimulants during the past year.[20]

Addiction

The question of whether or not MPH use in children leads to future addictive tendencies has sparked many inquiries and analyses. One study examined the history of a group of adults who had used cocaine at least once, and found that those who as children had been medically diagnosed with hyperactivity and had received methylphenidate treatment for between one and ten years had a percentage of cocaine abuse twice that of either of two control groups: one group of same-age individuals who had not been diagnosed with hyperactivity, and one group of individuals who had also been diagnosed with hyperactivity but had not been treated with stimulants. This research has been described as indicating that "... methylphenidate was still capable of explaining a small but significant proportion of the variance in cocaine use even after approximately 15 years."[21] On the flip side, a 2003 project suggests that boys with ADHD who are treated with stimulants like MPH are actually less likely to abuse drugs (including alcohol) later in life.[22]

Long-term effects

Ritalin has been used on a long-term basis since the mid-20th century, yet clinical studies of the long-term use effects have not been undertaken. A great deal of controversy has been generated by non-expert groups, many of them basing 'research' on the negative effects of ritalin on children. Many of these reports have been forwarded by Scientology-related groups.

In a 2005 study, no "clinically significant" effects on growth, vital signs, tics, or laboratory tests (including urinalysis, hematology/complete blood counts, electrolytes, and liver function tests) were observed after 2 years of treatment. [23]

Still, some theoretical studies raise theoretical questions. For example, Adriani et al (2005) found plastic changes in reward related behavior in rats after they were in a drug-free state. [24] Whether or not this would have any effect on human cognition is unknown.

Effects on stature

Researchers have also looked into the role of methylphenidate in affecting stature, with some studies finding slight decreases in height acceleration. [25] Other studies indicate height may normalize by adolescence. [26][27]

Risk of death

As mentioned above, methylphenidate has been implicated in cases of sudden death by heart failure. The FDA decided against requiring warning labels, even though its advisory committee voted in favor of this. According to the Merck Index Methylphenidate had an LD***50*** of 150mg/kg body mass.

Potential Carcinogen

In February 2005, a team of researchers from The University of Texas M.D. Anderson Cancer Center led by R.A. El-Zein announced that a small scale study of 12 children indicated that methylphenidate may be carcinogenic. In the study, 12 children were given standard therapeutic doses of methylphenidate. At the conclusion of the 3 month study, all 12 children displayed significant, treatment induced chromosomal aberrations. The researchers indicated that while their study was relatively small, they indicated the results should be reproduced one more time in a bigger population for a definitive conclusion about the genotoxicity of methylphenidate to be drawn. The link between chromosomal aberrations and cancer risk has been established. [28]

The results are controversial, however, since there have been conflicting results regarding the mutagenicity of methylphenidate.

A 2003 study tested the effects of d-methylphenidate (Focalin), l-methylphenidate, and d,l-methylphenidate (Ritalin) on mice to search for any carcinogenic effects. The researchers found that all three compounds were non-genotoxic and non-clastogenic; d-MPH, d,l-MPH, and l-MPH did not cause mutations or chromosome aberrations. They concluded that none of the compounds present a carcinogenic risk to humans. [29]

In 2005, the U.S. Food and Drug Administration issued a series of public health advisories warning that Ritalin and its sister drugs may cause visual hallucinations, suicidal thoughts, psychotic behavior, as well as agression or violent behavior.

Illicit use

Both the United States Drug Enforcement Administration (DEA) and the United Nations International Narcotics Control Board have expressed concern about the ease with which legally prescribed MPH is diverted to the illicit market.[30][31]

According to the DEA, "The increased use of this substance [MPH] for the treatment of ADHD has paralleled an increase in its abuse among adolescents and young adults who crush these tablets and snort the powder to get high. Youngsters have little difficulty obtaining methylphenidate from classmates or friends who have been prescribed it."[32]

Street names for Ritalin include: diet coke, kiddie cocaine, kiddie coke, vitamin R, R-ball, poor man's cocaine, rids, skittles, and smarties.

See also

- Phenethylamines
- Psychoactive drug
- Stimulant
    - Amphetamine
- Methamphetamine
- Benzedrine
    - Attention Deficit Disorder

Footnotes

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Psychedelics, dissociatives and deliriants

Certain drugs can affect the subjective qualities of perception, thought or emotion, resulting in altered interpretations of sensory input, alternate states of consciousness, or hallucinations. This general group of pharmacological agents can be divided into three broad categories: *psychedelics*, *dissociatives* and *deliriants*. All of these agents act as neurotransmitter mimics, often as agonists or antagonists at neurotransmitter receptors. Their primary effects are markedly different from those of other psychoactives such as cocaine, Amphetamine, heroin or alcohol.

The term *hallucinogen* is often broadly applied, especially in current scientific literature, to some or all of these substances. The term, though, has long attracted criticism. (See Etymology and alternative terms)

Despite the use of "hallucinogen" as a cover term, true hallucinations, as distinct from illusions, are rare with these substances. The apparent unity of the category is further belied by the quite different effects of psychedelics, dissociatives, and deliriants on consciousness. Broadly speaking, psychedelics reduce the filters in the brain causing sensory overload which is often manifested in visual and audial distortion, dissociatives cause a separation between cognition and sensory awareness (possibly including hallucination or dreamlike experiences), and deliriants are a class of drug that produce a fragmented dissociated state of quasi-consciousness akin to sleepwalking where dreams and reality intertwine to produce potentially dangerous hallucinations indistinguishable from reality.

These substances have a millennial history of traditional use in medicine and religion, where they have been prized as means to access spiritual realities and to promote physical and mental healing. Together with other plant agents, like tobacco, they are important tools of shamans and other hierophants. Native American practitioners using peyote have reported success in treating alcoholism, and Mazatec practitioners routinely use psilocybin mushrooms for healing and divination.

Psychedelics

Main article: psychedelic drug

The psychedelic (mind manifesting) drugs are classified as those whose primary action is that of enhancing or amplifying the thought processes of the brain. One prominent psychological explanation of psychedelics' effects is the "reducing valve" hypothesis, derived from Aldous Huxley's reflections on his experiments with mescaline. In this view, the drugs disable the brain's experiential "filters," which block or suppress unimportant or undesired signals to the conscious mind from other parts of the brain, including but not limited to the senses, emotions, memories and the unconscious (or subconscious) mind. This effect has

been described as mind expanding, or consciousness expanding as the conscious mind becomes aware of (or sometimes assaulted by) things normally inaccessible to it. At high levels this can become overwhelming, and can result in a dissociative state whereby one is so occupied by their racing thoughts that they lose touch with the outside world during the peak of the experience.

Classic psychedelics include LSD (acid), psilocybin (psychedelic mushrooms), mescaline (peyote), LSA (morning glory seeds) and also Ayahuasca (yage). Some of the synthetic "club drugs" such as MDMA ('pure' ecstasy), 2C-B (nexus), DOM (STP) and 5-MeO-DIPT (Foxy Methoxy) which have much more specific action to particular aspects of the psyche are also classed as psychedelics, as well as cannabis (marijuana).

Some psychedelics (namely LSD, psilocybin and cannabis) are extremely non-toxic, making it difficult to overdose unless these compounds are combined with other drugs.

Dissociatives

Main article: dissociative drug

A dissociative is a drug which reduces (or blocks) signals to the conscious mind from other parts of the brain, typically (but not necessarily, or limited to) the physical senses. Such a state of sensory deprivation can *facilitate* self exploration, hallucinations, and dreamlike states of mind which may resemble some psychedelic mindstates. Essentially similar states of mind can be reached via contrasting paths -- psychedelic or dissociative. That said, the entire experience, risks and benefits are markedly different.

The primary dissociatives are similar in action to PCP (angel dust) and include Ketamine (an anaesthetic), and DXM (an active ingredient in many cough syrups, dextromethorphan). Also included are nitrous oxide, salvia divinorum, and muscimol from the amanita muscaria (fly agaric) mushroom.

Many dissociatives also have CNS depressant effects, thereby carrying similar risks as opioids to slowing breathing or heart rate to levels resulting in death (when using very high doses). This does not appear to be true in other cases, toxic effects do not appear to exist in the case of salvia divinorum, and the principal risk of nitrous oxide seems to be due to oxygen deprivation. Injury from falling is also a danger, as nitrous oxide may cause sudden loss of consciousness, an effect of oxygen deprivation. Long term use of dissociative anesthetics such as PCP and Ketamine (and possibly DXM) have been suspected to cause Olney's lesions, though these lesions have never been demonstrated in primates to date.

Deliriants

Main article: Deliriant

The deliriants (or anticholinergics) are a special class of dissociative which are antagonists for the acetylcholine receptors (unlike muscarine and nicotine which are agonists of these receptors). Deliriants are considered to be true hallucinogens as users will have conversations with people who aren't there, or become angry with a 'person' mimicking their actions, not realizing it is their own reflection in a mirror (which could be dangerous if

they became aggressive towards a glass mirror). While the regular dissociatives can produce effects similar to lucid dreaming (where one is consciously aware they are dreaming), the deliriants have effects akin to sleepwalking (where one doesn't remember what transpired during the experience).

Included in this group are such plants as deadly nightshade, mandrake, henbane and datura, as well as a number of pharmaceutical drugs when taken in very high doses such as the antihistamine diphenhydramine (Benadryl) and the antiemetic dimenhydrinate (Dramamine or Gravol).

In addition to the danger of being far more "out of it" than with other drugs, and retaining a truly fragmented dissociation from regular consciousness without being immobilized, the anticholinergics are toxic, can cause death due to overdose, and also include a number of uncomfortable side effects. These side effects include dehydration and mydriasis.

Etymology and alternative terms

A variety of different, imprecise terms have also been used to refer to drugs of this type. One of the first terms used in English to describe these substances was "Phantastica", coined in 1928 by Louis Lewin in his ground-breaking monograph of the same name. The term was applied to plants that "bring about evident cerebral excitation in the form of hallucinations, illusions and visions ... followed by unconsciousness or other symptoms of altered cerebral functioning." Lewin complained that the word "does not cover all that I should wish it to convey", and indeed with the advent of the discovery of LSD and the widespread scientific experimentation with it and similar drugs, numerous supposedly improved terms were constructed, including hallucinogen, psychedelic, psychotomimetic, psycholytic, schizophrenogenic, cataleptogenic, mysticomimetic and psychodysleptic.

Of all the terms created, "hallucinogen", meaning roughly "generating delusions and false notions" (particularly in the form of sensory distortions), probably enjoys the most widespread and accepted usage. "Psychedelic", meaning "mind manifesting" and emphasizing the introspective potential of the drugs, and "entheogen", meaning "becoming divine within", are also widely used, particularly among those with positive attitudes towards their usage. In some cases, authors who otherwise use these terms have felt themselves pressured to use "hallucinogen" or "psychotomimetic" (or sometimes "psychomimetic", in either case meaning "mimicking psychosis") in scientific publications. The terms "empathogen" and "entactogen" (see empathogen-entactogen) are also applied to certain drugs (notably those similar to MDMA) that are also sometimes classed as hallucinogens.

Many different names have been proposed over the years for this drug class. The famous German toxicologist Louis Lewin used the name phantastica earlier in this century, and as we shall see later, such a descriptor is not so farfetched. The most popular names, hallucinogen, psychotomimetic, and psychedelic ("mind manifesting"), have often been used interchangeably. Hallucinogen is now, however, the most common designation in the scientific literature, although it is an inaccurate descriptor of the actual effects of these drugs. In the lay press, the term psychedelic is still the most popular and has held sway for nearly four decades. Most recently, there has been a movement in nonscientific circles to recognize the ability of these substances to provoke mystical experiences and evoke feelings of

spiritual significance. Thus, the term entheogen, derived from the Greek word entheos, which means "god within," was introduced by Ruck et al. and has seen increasing use. This term suggests that these substances reveal or allow a connection to the "divine within." Although it seems unlikely that this name will ever be accepted in formal scientific circles, its use has dramatically increased in the popular media and on internet sites. Indeed, in much of the counterculture that uses these substances, entheogen has replaced psychedelic as the name of choice and we may expect to see this trend continue.

—David E. Nichols: "Hallucinogens", Pharmacol Ther 101(2):131-181[1]

The World Health Organization effectively endorses the "psychotomimetic" point of view, defining a hallucinogen as "a chemical agent that induces alterations in perception, thinking, and feeling which resemble those of the functional psychoses without producing the gross impairment of memory and orientation characteristic of the organic syndromes." [2]

History of use

Hallucinogenic drugs are among the oldest drugs used by humankind, as hallucinogens naturally occur in mushrooms, cacti, and various other plants. Whether the use of hallucinogens is encouraged, unregulated, regulated, or prohibited, and whether hallucinogens are used for recreational, medicinal, or spiritual purposes, varies from culture to culture and nation to nation. In most nations of the world, the possession of many hallucinogens, even those that are common in nature, is a crime punished by fines, imprisonment or in many countries, death. For some religious purposes, however, there are exceptions. For instance, though possession of peyote cactus is illegal for most purposes in the United States, American Courts have upheld the Constitutional right of Native Americans to grow and consume peyote.

Traditional religious and shamanic use (entheogens)

In human culture hallucinogens have historically most commonly been used in the setting of religious or shamanic rituals. In this context they are more precisely referred to as entheogens, and are used to facilitate healing, divination, communication with the spirits, and coming of age ceremonies. Evidence exists for the use of entheogens in prehistoric times, as well as in numerous ancient cultures, including the Ancient Egyptian, Mycenaean, Ancient Greek, Vedic, Maya, Inca the and Aztec cultures, not to mention the Upper Amazon, arguabaly the region of globe where entheogens have assumed--literally over millennia--the greatest symbolic and sacred import, as noted among the Urarina of Peruvian Amazonia, who continue to practice an elaborate system of ayahuasca shamanism, coupled with animistic religious beliefs.

The rise of the Abrahamic religions (Judaism, Christianity and Islam) caused a decline of entheogen use in their area. Witness the destruction of the Eleusinian Mysteries, or the Great Witch Hunt of the Early Modern Age, in which practitioners of entheogenic rites in Western Europe were accused of associating with the Devil. Nevertheless, some (mainly tribal) cultures have survived this (ongoing) assault and still practise entheogen use. In others, non-religious hallucinogen use, while not exactly encouraged, is tolerated and not seen as

uncommon. Present-day, historical and mythological aspects of entheogens are discussed in the entry entheogen.

Early scientific investigations

Although natural hallucinogenic drugs have been known to mankind for millennia, it was not until the early 20th century that they received extensive attention from Western science. Earlier beginnings include scientific studies of nitrous oxide in the late 18th century, and initial studies of the constituents of the peyote cactus in the late 19th century. Starting in 1927 with Kurt Beringer's Der Meskalinrausch (The Mescaline Intoxication), more intensive effort began to be focused on studies of psychoactive plants. Around the same time, Louis Lewin published his extensive survey of psychoactive plants, Phantastica (1928). Important developments in the years that followed included the re-discovery of Mexican magic mushrooms (in 1936 by Robert J. Weitlaner) and ololiuhqui (in 1939 by Richard Evans Schultes). Arguably the most important pre-World War II development was by Albert Hofmann's 1938 invention of the semi-synthetic drug LSD, which was later discovered to produce hallucinogenic effects, in 1943.

Hallucinogens after World War II

After World War II there was an explosion of interest in hallucinogenic drugs in psychiatry, owing mainly to the discovery of LSD. Interest in the drugs tended to focus on either the potential for psychotherapeutic applications of the drugs (see psychedelic psychotherapy), or on the use of hallucinogens to produce a "controlled psychosis", in order to understand psychotic disorders such as schizophrenia. Between the mid 1950s and the mid 1960s over 1000 scholarly articles were published on hallucinogen research. Hallucinogens were also researched in several countries for their potential as agents of chemical warfare. Most famously, several tragic incidents associated with the CIA's MK-ULTRA mind control research project have been the topic of media attention and lawsuits.

At the beginning of the 1950s, the existence of hallucinogenic drugs was virtually unknown among the general public of the West. However this soon changed as several influential figures were introduced to the hallucinogenic experience. Aldous Huxley's 1953 essay The Doors of Perception, describing his experiences with mescaline, and R. Gordon Wasson's 1957 Life magazine article (Seeking the Magic Mushroom) brought the topic into the public limelight. In the early 1960s countercultural icons such as Timothy Leary, Allen Ginsberg and Ken Kesey advocated the drugs for their psychedelic effects, and a large subculture of psychedelic drug users was spawned. Many people argue that psychedelic drugs played a major role in catalyzing the vast social changes initiated in the 1960s. As a result of the growing popularity of LSD, and, some contend, establishment disdain for the hippies with whom it was heavily associated, LSD was banned in the United States in 1967.

Social status of hallucinogens

After the fading from public sight as one of the many elements of the 1960s counterculture, hallucinogen use took a less visible but nevertheless persistent role in Western society in the 1970s and 1980s. In the 1990s and 2000s something of a revival of interest in the drugs has occurred. There are probably several important contributing factors to the resurgence. One is the rise of dance-based rave and trance culture, in which participants frequently employ drugs such as the entactogen MDMA, and to a lesser extent, other hallucinogenic drugs such as LSD, magic mushrooms and ketamine, as an aid to inducing ecstatic or trance states of consciousness. A second major contributing factor to the revival of interest in hallucinogenic drugs has been the advent of the Internet and World Wide Web. This has made information pertaining to drugs much more accessible to the general public, provided a platform for advocacy that was not previously available, and has enabled otherwise isolated interested parties to communicate and exchange information and experiences. Some well-known contemporary authors of topics relating to hallucinogens include Terence McKenna, Stanislav Grof, Alan Watts, Aldous Huxley, Timothy Leary, Alexander Shulgin, Jonathan Ott and Rick Strassman.

Legal status

As of 2004, most well known hallucinogens (aside from DXM) are illegal in most Western countries. One notable exception to the current criminalization trend is in parts of Western Europe, especially in the Netherlands, where hallucinogenic mushrooms are considered to be so-called "soft drugs", along with cannabis. While the possession of soft drugs is technically illegal, the Dutch government has decided that using law enforcement to combat their use is largely a waste of resources. As a result, public "coffeeshops" in the Netherlands openly sell cannabis, and "smart shops" sell drugs like psilocybin mushrooms and ayahuasca for personal use (See Drug policy of the Netherlands).

Since the latter part of the twentieth century, this attitude has spread throughout Europe; many European countries no longer actively pursue anti-drug policies, and rarely enforce extant legal penalties for personal-use quantities of hallucinogenic drugs. This is especially true with mild hallucinogens such as cannabis, which is rapidly gaining acceptance in western Europe as a harmless and socially acceptable intoxicant, much as alcohol is considered throughout the West. Despite being scheduled as a controlled substance in the mid 1980s, ecstasy's popularity has been growing since that time in western Europe and in the United States.

Attitudes towards hallucinogens other than cannabis have been slower to change. Several attempts to change the law on the grounds of freedom of religion have been made. Some of these have been successful, for example the Native American Church in the United States, and Santo Daime in Brazil. Some people argue that a religious setting should not be necessary for the legitimacy of hallucinogenic drug use, and for this reason also criticize the euphemistic use of the term "entheogen". Non-religious reasons for the use of hallucinogens including spiritual, introspective, psychotherapeutic, recreational and even hedonistic motives, each subject to some degree of social disapproval, have all been defended as the legitimate exercising of civil liberties, including freedom of thought and freedom of self-harm.

Many connect the idea of being "high" or going through a psychedelic state, as having brain damage or going crazy. This is due to the effect of the drug which, in some cases, can be overwhelming. Effects of these drugs can mimic psychological conditions such as psychosis, schizophrenia, and thought disorder. However, this is largely a misconception of the psychedelic state. After many studies investigating its possible use as a "psychotomimetic" and decades of personal/spiritual use it has become apparent that the psychedelic state is wholly different from a psychotic state and thus is ill-compared to schizophrenia and other mental disorders.

Several medical and scientific people, including Albert Hofmann, advocate the drugs should not be banned, but should be strongly regulated like opiates and warn they can be dangerous without proper psychological supervision. [3] Taking a hallucinogenic drug without knowledge can result in psychological trauma, and has occurred many times because many psychedelic drugs such as LSD have low dose and can easily be added to food or drink, similar to "date rape drugs" or Mickey Finns, and those who deliberately do that can be charged with assault. (These occurrences have created some urban myths such as the blue star tattoo myth).

Pharmacology

Hallucinogens can be classified by quality of action, mechanisms of action, or by chemical structure. These classifications often correlate to some extent. The classification system below attempts to blend these three approaches in order to create a balanced and simple overview that is as clear and easy to grasp as possible.

Almost all hallucinogens contain nitrogen and are therefore classified as alkaloids. THC and Salvinorin A are exceptions. Many hallucinogens have chemical structures similar to those of human neurotransmitters, such as serotonin, and temporarily modify the action of neurotransmitters and/or receptor sites.

A classical classification is that of Lewin (Phantastica, 1928): Class I Phantastica roughly correspond to the psychedelics, which is a more modern term usually used as synonym to "hallucinogen" by people with positive attitudes towards them. Here the term is used a bit differently to discriminate one particular class of hallucinogens which it seems to describe best. They typically have no sedative effects (sometimes the opposite) and there is usually a clearcut memory to their effects.

Class II Phantastica correspond to the other classes in this scheme. They tend to sedate in addition to their hallucinogenic properties and there often is an impaired memory trace after the effects wear off.

Psychedelics and mental illnesses in long-term users

Most psychedelics are not known to have long-term physical toxicity. However, amphetamine-like psychedelics, such as MDMA, that release neurotransmitters may stimulate increased formation of free radicals possibly formed from neurotransmitters released from the synaptic vesicle. Free radicals are associated with cell damage in other contexts, and have been suggested to be involved in many types of mental conditions including Parkinson's disease, senility, schizophrenia, and Alzheimer's. Research on this question has not reached a firm conclusion. The same concerns do not apply to psychedelics that do not release neurotransmitters, such as LSD, nor to dissociatives and deliriants.

No clear connection has been made between psychedelic drugs and organic brain damage; however, high doses over time of some dissociatives and deliriants have been shown to cause Olney's lesions in animals, and have been suspected to occur in humans. Additionally, Hallucinogen persisting perception disorder (HPPD) is a diagnosed condition where some effects of drugs persist after a long time--although medical technology has yet to determine what causes the condition.

Pharmacological classes of hallucinogens

Psychedelics (serotonin 5-HT2A receptor agonists)

- Tryptamines
    - Lysergamides

- Phenethylamines
    - Substituted phenethylamines
    - Substituted Amphetamine
        - Empathogens and/or Entactogens **(serotonin releasers)**
- Cannabinoids (CB-1 cannabinoid receptor agonists)

Dissociatives

- NMDA receptor antagonists and sigma***1*** ligands
- Kappa opioid receptor agonists
- Inhalants
- Cholinergics

Deliriants (**anticholinergics**)

- Tropanes
- Antihistamines

Hallucinogenic plants, fungi, and animals

Among the best-known hallucinogenic plants and fungi are:

Plants

Psychedelics

- Ayahuasca (contains DMT and an MAOI, commonly Banisteriopsis caapi with Psychotria viridis)
- Epená (Virola sp.) (contains 5-MeO-DMT and DMT)
- Hawaiian baby woodrose (Argyreia nervosa) (contains Ergine)
- Ololiuhqui/Coaxihuitl (Turbina/Rivea corymbosa) (contains Ergine)
- Tlitliltzin/Badoh Negro (Ipomoea violacea) (contains Ergine)
- Iboga (Tabernanthe iboga) (contains ibogaine)

Cacti psychedelics

- Peruvian Torch cactus (Trichocereus peruvianus) (contains mescaline)
- Peyote cactus (Lophophora williamsii) (contains mescaline)
- San Pedro cactus (Trichocereus pachanoi) (contains mescaline)

Quasi-psychedelics

- Cannabis (contains THC)
- Sinicuichi (Heimia salicifolia) (questioned hallucinogenic activity)
- Nutmeg (Myristica fragrans) (hallucinogenic activity results from ingestion of massive doses of this spice)

Dissociatives

- Diviner's sage (Salvia divinorum) (contains salvinorin A)

Deliriants

- Deadly nightshade (Atropa belladonna) (contains tropane alkaloids) Floripondio (Brugmansia sp.) (contains tropane alkaloids) Henbane (Hyoscyamus niger) (contains tropane alkaloids) Mandrake (Mandragora sp.) (contains tropane alkaloids) Thorn Apple/Jimson Weed (Datura sp.) (contains tropane alkaloids)

Fungi

Psychedelics

- Psilocybe mushrooms (Psilocybe sp. and some Conocybe, Panaeolus and Stropharia) (contain psilocybin and psilocin)
- Ergot fungus (Claviceps purpurea) (not hallucinogenic in itself, but contains LSD precursors)

Dissociatives

- Fly Agaric mushroom (Amanita muscaria) (contains muscimol)

Animals

Psychedelics

- Psychoactive toads (Bufo alvarius) (contain 5-MeO-DMT and Bufotenine)

See also

- Entheogen

- Psychedelic mushroom
- Hard and soft drugs

Notes

1. ^ [1]

Entactogens and Empathogens

The terms *empathogen* and *entactogen* are different terms used to describe a class of psychoactive drugs that produce distinctive emotional and social effects similar to MDMA ("ecstasy"). Other members of this class are MDA, MDEA, MBDB, and AET . Entactogens are often incorrectly referred to as hallucinogens or stimulants. The chemical structure of most entactogens contains a substituted Amphetamine core.

The term "*empathogen*" was coined in 1983 by Ralph Metzner to denote chemical agents inducing feelings of empathy.

"*Entactogen*" was coined by David E. Nichols as an alternative to "empathogen", attempting to avoid the potential for improper association of the latter with negative concepts related to the Greek root "pathos" (suffering); Nichols also thought the word was limiting, and did not cover other therapeutic uses for the drugs which go beyond instilling feelings of empathy. The word "entactogen" is derived from the roots "en" (Greek: within), "tactus" (Latin: touch) and "gen" (Greek: produce). Neither term is dominant in usage, and despite their difference in connotation are essentially interchangeable as they refer to precisely the same chemicals.

These drugs appear to produce a different spectrum of psychological effects from stimulants such as methamphetamine and Amphetamine or from psychedelic drugs such as LSD or Psilocybin. As implied by the category names, users of entactogens say the drugs often produce feelings of empathy, love, and emotional closeness to others. However, there have been only very preliminary comparisons of these different drugs in humans in properly controlled laboratory studies.

If MDMA is taken as a representative entactogen, the pharmacological mechanisms of this class appear to resemble those of methamphetamine. Extracellular dopamine, serotonin, and norepinephrine are all increased by both MDMA and methamphetamine. However, entactogens other than MDMA have received relatively little scientific attention, making it difficult to draw conclusions about the mechanisms of entactogens in general. It is also unknown why entactogens might produce emotional effects that differ from stimulants.

References

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- Nichols, D.E. Differences between the mechanism of action of MDMA, MBDB, and the classic hallucinogens. Identification of a new therapeutic class: entactogens 1986 J Psychoactive Drugs 18 305-13

See also

- Phenethylamine
- Entheogen

Entheogens

An *entheogen*, in the strictest sense, is a psychoactive substance (most often some plant matter with hallucinogenic effects) that occasions an enlightening spiritual or mystical experience, within the parameters of a cult, in the original non-pejorative sense of cultus. In a broader sense, the word "entheogen" refers to artificial as well as natural substances that induce alterations of consciousness similar to those documented for ritual ingestion of traditional shamanic inebriants, even if it is used in a secular context.

The word *entheogen* is a modern term derived from two Ancient Greek words, ½¸µ¿Â (entheos) and ³µ½Ã¸±¹ (genesthai). Entheos literally means "god (theos) within", more freely translated "inspired". The Greeks used it as a term of praise for poets and other artists. Genesthai means "to cause to be" or becoming. So an entheogen is "that which causes God (or godly inspiration) to be within a person".

Terminology and uses of the word

The word "entheogen" was coined in 1979 by a group of ethnobotanists and scholars of mythology (Carl A. P. Ruck, Jeremy Bigwood, Danny Staples, Richard Evans Schultes, Jonathan Ott and R. Gordon Wasson). The literal meaning of the word is "that which causes God to be within an individual". The translation "creating the divine within" is sometimes given, but it should be noted that entheogen implies neither that something is created (as opposed to just perceiving something that is already there) nor that that which is experienced is within the user (as opposed to having independent existence).

The term was coined as a replacement for the terms "hallucinogen" (popularized by Aldous Huxley's experiences with mescaline, published as The Doors of Perception in 1953) and "psychedelic" (a Greek neologism for "soul-revealing", coined by psychiatrist Humphry Osmond, who was quite surprised when the well-known author, Aldous Huxley, volunteered to be a subject in experiments Osmond was running on mescaline). Ruck et al. argued that the term "hallucinogen" was inappropriate due to its etymological relationship to words

relating to delirium and insanity. The term "psychedelic" was also seen as problematic, due to the similarity in sound to words pertaining to psychosis and also due to the fact that it had become irreversibly associated with various connotations of 1960s pop culture.

The meanings of the term "entheogen" were formally defined by Ruck et al.:

> In a strict sense, only those vision-producing drugs that can be shown to have figured in shamanic or religious rites would be designated entheogens, but in a looser sense, the term could also be applied to other drugs, both natural and artificial, that induce alterations of consciousness similar to those documented for ritual ingestion of traditional entheogens.

Since 1979, when the term was proposed, its use has become widespread in certain circles. In particular, the word fills a vacuum for those users of entheogens who feel that the term "hallucinogen", which remains common in medical, chemical and anthropological literature, denigrates their experience and the world view in which it is integrated. Use of the strict sense of the word has therefore arisen amongst religious entheogen users, and also amongst others who wish to practice spiritual or religious tolerance.

The use of the word "entheogen" in its broad sense as a synonym for "hallucinogenic drug" has attracted criticism on three grounds:

- On pragmatic grounds, the objection has been raised that the meaning of the strict sense of "entheogen", which is of specific value in discussing traditional, historical and mythological uses of entheogens in religious settings, is likely to be diluted by widespread, casual use of the term in the broader sense.
- Secondly, some people object to the misuse of the root theos (god in ancient Greek) in the description of the use of hallucinogenic drugs in a non-religious context, and coupled with the climate of religious tolerance or pluralism that prevails in many present-day societies, the use of the root theos in a term describing non-religious drug use has also been criticised as a form of taboo deformation.
- Thirdly, there are some substances that at least partially fulfil the definition of an entheogen that is given above, but are not considered hallucinogenic in the usual sense. One important example is the bread and wine of the Christian (especially Roman Catholic and Episcopal) Eucharist. The 'bread' and 'wine' of early Christianity were discussed and treated in a way that fits the description of an entheogenic substance; ingesting the Eucharist induced the Holy Spirit, as a shared unity-experience in the mystic altered state.

Ideological objections to the broad use of the term often relate to the widespread existence of taboos surrounding psychoactive drugs, with both religious and secular justifications. The perception that the broad sense of the term "entheogen" is used as a euphemism by hallucinogenic drug-users bothers both critics and proponents of the secular use of hallucinogenic drugs. Critics frequently see the use of the term as an attempt to obscure what they perceive as illegitimate motivations and contexts of secular drug use. Some proponents also object to the term, arguing that the trend within their own subcultures and in the scientific literature towards the use of term "entheogen" as a synonym for "hallucinogen" devalues the positive uses of drugs in contexts that are secular but nevertheless, in their view, legitimate.

Beyond the use of the term itself, the validity of drug-induced, facilitated, or enhanced religious experience has been questioned. The claim that such experiences are less valid than religious experience without the use of any chemical catalysts faces the problem that the descriptions of religious experiences by those using entheogens are indistinguishable from many reports of religious experiences without drugs. In an attempt to empirically answer the question about whether drugs can actually facilitate religious experience, the Marsh Chapel Experiment was conducted by physician and theology doctoral candidate, Walter Pahnke, under the supervision of Timothy Leary and the Harvard Psilocybin Project. In the double-blind experiment, volunteer graduate school divinity students from the Boston area almost all claimed to have had profound religious experiences under the influence of psilocybin. (A brief video about the Marsh Chapel experiment can be viewed here.)

In 2006, a more rigorously controlled version of this experiment was conducted at John Hopkins University, yielding very similar results.[1]

Use of entheogens

Naturally occurring entheogens such as Psilocybin and Dimethyltryptamine were, for the most part, discovered and used by older cultures, as part of their spiritual and religious life, as plants and agents which were respected, or in some cases revered. By contrast, artificial and modern entheogens, such as MDMA, never had a tradition of religious use.

Currently entheogens are used in three principal ways: as part of established traditions and religions, secularly for personal spiritual development, and secularly in a manner similar to recreational drugs. A lesser use of entheogens for medical and therapeutic use is rarely pursued due to legislative and cultural objections.

Entheogen-using cultures

The use of entheogens in human cultures is generally ubiquitous throughout recorded history. The number of entheogen-using cultures is therefore very large. Some of the instances better known to Western scholarship are discussed here.

Africa

The best-known entheogen-using culture of Africa is the Bwitists, who used a preparation of the root bark of Iboga (Tabernanthe iboga).[1] A famous entheogen of ancient Egypt is the blue lotus (Nymphaea caerulea). There is evidence for the use of entheogenic mushrooms in Côte d'Ivoire (Samorini 1995). Numerous other examples of the use of plants in shamanic ritual in Africa are yet to be investigated by western science.

Americas

Entheogens have played a pivotal role in the spiritual practices of most American cultures for millennia. The first American entheogen to be subject to scientific analysis was the peyote cactus (Lophophora williamsii). For his part, one of the founders of modern ethno-botany,

the late Richard Evans Schultes of Harvard University documented the ritual use of peyote cactus among the Kiowa of Oklahoma. Used traditionally by many cultures of what is now Mexico, its use spread to throughout North America in the 19th century, replacing the toxic entheogen Sophora secundiflora (mescal bean). Other well-known entheogens used by Mexican cultures include psilocybin mushrooms (known to the Aztecs under the Nahuatl name teonanacatl), the seeds of several morning glories (Nahuatl: tlitliltzin and ololiuhqui) and Salvia divinorum (Mazateco: Ska Pastora; Nahuatl: pipiltzintzintli).

Indigenous peoples of South America employ a wide variety of entheogens. Better-known examples include ayahuasca (Banisteriopsis caapi plus admixtures) among indigenous peoples (such as the Urarina) of Peruvian Amazonia. Other well-known entheogens include: borrachero (Brugmansia spp); San Pedro Trichocereus spp); and various tryptamine-bearing snuffs, for example Epená (Virola spp), Vilca and Yopo (Anadananthera spp). The familiar tobacco plant, when used uncured in large doses in shamanic contexts, also serves as an entheogen in South America. Also, a tobacco that contains higher nicotine content, and therefore smaller doses required, called Nicotiana rustica was commonly used.

In addition to indigenous use of entheogens in the Americas, one should also note their important role in contemporary religions movements, such as the Rastafari movement and the Church of the Universe.

Asia

The indigenous peoples of Siberia (from whom the term shaman was appropriated) have used the fly agaric mushroom (Amanita muscaria) as an entheogen. The ancient inebriant Soma, mentioned often in the Vedas, may have been an entheogen. (In his 1967 book, Wasson argues that Soma was fly agaric. The active ingredient of Soma is presumed by some to be Ephedrine, an alkaloid with stimulant and (somewhat debatable) entheogenic properties derived from the soma plant, identified as Ephedra pachyclada.) However, there are also arguements to suggest that Soma could have also been Syrian Rue, Cannabis, or some combination of any of the above plants. Owing to a lack of clear chemical or even anecdotal information regarding the active ingredient(s) or effects of Soma, this debate is one which is unlikely to be completely and undisputably resolved

Europe

The use of entheogens in Europe was all but eliminated with the rise of post-Roman Christianity and especially during the great witch hunts of Early Modernity. European witches used various entheogens, including deadly nightshade (Atropa belladonna), mandrake (Mandragora officinarum) and henbane (Hyoscyamus niger). These plants were used, among other things, for the manufacture of "flying ointments". In Christian society, witches were commonly believed to fly through the air on broomsticks after coating them with the ointment and applying them to the skin. Consequently, any association with these plants could have proven extremely dangerous and lead to one's execution as a practitioner of witchcraft. The imposition of Roman Christianity also saw the end of the two-thousand-year-old tradition of the Eleusinian Mysteries, the initiation ceremony for the cult of Demeter

and Persephone involving the use of a possibly entheogenic substance known as kykeon. Similarly, there is evidence that nitrous oxide or ethylene may have been in part responsible for the visions of the equally long-lived Delphic oracle (Hale et al., 2003).

In the Christian era the Eucharist plays a symbolic role in religious tradition that has occasionally attracted the label of "entheogen" or "placebo entheogen", even though it does not conform to the original definition involving the use of vision-inducing substances.

Middle East

The entheogenic use of substances, particularly hashish, by ancient Sufis is well-documented. Its use by the "Hashshashin" to stupefy and recruit new initiates was widely reported during the Crusades. However, the drug used by the Hashshashin was likely wine, opium, henbane, or some combination of these, and, in any event, the use of this drug was for stupefaction rather than for entheogenic use. It has been suggested that the ritual use of small amounts of Syrian Rue is an artifact of its ancient use in higher doses as an entheogen. John Marco Allegro has argued in his book The Sacred Mushroom and the Cross that early Jewish and Christian sects and cults were based on the use of Amanita muscaria,[2] though this hypothesis has not achieved widespread currency.

Oceania

Indigenous Australians are generally supposed not to have used entheogens, although there is a strong barrier of secrecy surrounding Aboriginal shamanism, which has likely limited what has been told to outsiders. Natives of Papua New Guinea are known to use several species of entheogenic mushrooms (Psilocybe spp, Boletus manicus).[3] It has been suggested that the Mori of New Zealand used Mori Kava (Macropiper excelsum) as an entheogen (Bock 2000).

"Entheogen" in the Archaeological Record

There have been several examples of the use of Entheogens in the Archaeological Record, but many reports and studies are largley viewed as Psuedoscience. Many of these researchers, like R.G. Wasson or Giorgio Samorini, have produced a plethora of research but are not widley accepted by academia, largley being cited by fringe groups. The first direct evidence of entheogen use comes from Tassili, Algeria, with a cave painting of a mushroom-man, dating to 8000 BP.

"Entheogen" in Classical mythology and cult

Although entheogens are taboo in Christian and Islamic societies, their ubiquity and prominence in the spiritual traditions of other cultures is unquestioned. The entheogen, "the spirit, for example, need not be chemical, as is the case with the ivy and the olive: and yet the god was felt to be within them; nor need its possession be considered something detrimental, like drugged, hallucinatory, or delusionary: but possibly instead an invitation to knowledge or whatever good the god's spirit had to offer." (Ruck and Staples)

Most of the well-known modern examples, such as peyote, psilocybe and other psychoactive mushrooms and ololiuhqui, are from the native cultures of the Americas. However, it has also been suggested that entheogens played an important role in ancient Indo-European culture, for example by inclusion in the ritual preparations of the Soma, the "pressed juice" that is the subject of Book 9 of the Rig Veda. Soma was ritually prepared and

drunk by priests and initiates and elicited a paean in the Rig Veda that embodies the nature of an entheogen:

"Splendid by Law! declaring Law, truth speaking, truthful in thy works, Enouncing faith, King Soma!... O [Soma] Pavmana, place me in that deathless, undecaying world wherein the light of heaven is set, and everlasting lustre shines.... Make me immortal in that realm where happiness and transports, where joy and felicities combine..."

The Kykeon that preceded initiation into the Eleusinian Mysteries is another entheogen, which was investigated (before the word was coined) by Carl Kerenyí, in Eleusis: Archetypal Image of Mother and Daughter. Other entheogens in the Ancient Near East and the Aegean include the poppy, Datura, the unidentified "lotus" eaten by the Lotus-Eaters in the Odyssey and Narkissos.

According to Ruck, Eyan, and Staples, the familiar shamanic entheogen that the Indo-Europeans brought with them was knowledge of the wild Amanita mushroom. It could not be cultivated; thus it had to be found, which suited it to a nomadic lifestyle. When they reached the world of the Caucasus and the Aegean, the Indo-Europeans encountered wine, the entheogen of Dionysus, who brought it with him from his birthplace in the mythical Nysa, when he returned to claim his Olympian birthright. The Indo-European proto-Greeks "recognized it as the entheogen of Zeus, and their own traditions of shamanism, the Amanita and the 'pressed juice' of Soma — but better since no longer unpredictable and wild, the way it was found among the Hyperboreans: as befit their own assimilation of agrarian modes of life, the entheogen was now cultivable" (Ruck and Staples). Robert Graves, in his foreword to The Greek Myths, argues that the ambrosia of various pre-Hellenic tribes were amanita and possibly panaeolus mushrooms.

Amanita was divine food, according to Ruck and Staples, not something to be indulged in or sampled lightly, not something to be profaned. It was the food of the gods, their ambrosia, and it mediated between the two realms. It is said that Tantalus's crime was inviting commoners to share his ambrosia.

Christianity

Even in cultures where they are acceptable, improper use of an entheogen, by the unauthorized or uninitiated, has led to disgrace, exile, and even death. The expulsion of Adam and Eve from the Garden of Eden can be understood as such a parable of an entheogen misused, for the fruit of the Tree of Knowledge by its very nature is part of what is denoted by "entheogen":

"And the Lord God said, 'Behold, the man is become as one of us, to know good and evil: and now, lest he put forth his hand, and take also of the tree of life, and eat, and live for ever:' Therefore the Lord God sent him forth from the garden of Eden, to till the ground from whence he was taken. So he drove out the man; and he placed at the East of the garden of Eden cherubims and a flaming sword which turned every way, to keep the way of the tree of life." Genesis 3:23-25. (Such an interpretation would suggest that Christians are not to rehabilitate or help drug-users, a view not supported by many Christians.)

Indeed the entheogen offers godlike powers in many Traditional tales, including immortality. The failure of Gilgamesh in retrieving the plant of immortality from beneath the waters teaches that the blissful state cannot be taken by force or guile: when Gilgamesh lay on the bank, exhausted from his heroic effort, the serpent came and ate the plant.

Another attempt at subverting the natural order is told in a (according to some) strangely metamorphosed myth, in which natural roles have been reversed to suit the Hellenic world-view. The Alexandrian Apollodorus relates how Gaia (spelled "Ge" in the following passage), Mother Earth herself, has supported the Titans in their battle with the Olympian intruders. The Giants have been defeated:

"When Ge learned of this, she sought a drug that would prevent their destruction even by mortal hands. But Zeus barred the appearance of Eos (the Dawn), Selene (the Moon), and Helios (the Sun), and chopped up the drug himself before Ge could find it."

But what is essential in Christianity is the concept of "The Anointed" or Christ or Messiah, for the priests at first, Levites first of all, instated by Moses himself, and then later for Kings, particularly Saul, David and Solomon, and of course Prophets. This anointing with the "holy chrism" is a practice that must not be open to laymen. The recipe of this "chrism" is given in Exodus 30:22-33 and it contains one element known has "Kanah bosm", that is to say the blooms of a plant that is today identified as cannabis. One reference is essential in that field, even if there are a few mistakes or fuzzy elements in it: Chris Bennett and Neil McQueen, "Cannabis and the Christ: Jesus used Marijuana" on http://www.cannabisculture.com/backissues/cc11/christ.html.

We are then no longer dealing with a metaphor like the apple in the Garden of Eden but with a real phenomenon that can be studied in details.

—Apollodorus 1.34-38.

193.249.86.190 16:20, 12 November 2006 (UTC) Dr Jacques COULARDEAU, Université Paris Dauphine & Université Paris 1 Panthéon Sorbonne

Entheogens in literature

Consumption of the imaginary mushroom anochi as the entheogen underlying the creation of Christianity is the premise of Philip K. Dick's last novel, "The Transmigration of Timothy Archer".

Aldous Huxley's final novel, Island (1962), depicted a fictional entheogenic mushroom — termed "moksha medicine" — used by the people of Pala in rites of passage, such as the transition to adulthood and at the end of life.

In his book "The Sacred Mushroom and the Cross: A Study of the Nature and Origins of Christianity within the Fertility Cults of the Ancient Near East", [2] John M. Allegro argues etymologically that Christianity developed out of the use of a psychedelic mushroom, the true body of Christ, which was later forgotten by its adherents.

Bruce Sterling's "Holy Fire" novel refers to the religion in the future as a result of entheogens, used freely by the population.

References

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    - M. Bock 2000 "Mori kava (Macropiper excelsum)" in Eleusis n.s. vol 4 (no current url)
    - Plants of the Gods: Their Sacred, Healing and Hallucinogenic Powers by Richard Evans Schultes, Albert Hofmann, Christian Ratsch - ISBN 0-89281-979-0

End notes

1. ^ Bwiti: An Ethnography of the Religious Imagination in Africa **by James W. Fernandez, Princeton University Press, 1982**

2. ^ a b Allegro, John Marco (1970). The Sacred Mushroom and the Cross: A Study of the Nature and Origins of Christianity within the Fertility Cults of the Ancient Near East. Hodder and Stoughton. ISBN 0-340-12875-5.

3. ^ Benjamin Thomas Ethnobotany & Anthropology Research Page

1. ^ Bwiti: An Ethnography of the Religious Imagination in Africa **by James W. Fernandez, Princeton University Press, 1982**

2. ^ a b Allegro, John Marco (1970). The Sacred Mushroom and the Cross: A Study of the Nature and Origins of Christianity within the Fertility Cults of the Ancient Near East. Hodder and Stoughton. ISBN 0-340-12875-5.

3. ^ Benjamin Thomas Ethnobotany & Anthropology Research Page

Iboga

Scientific classification

Kingdom: Plantae
Division: Magnoliophyta
Class: Magnoliopsida
Order: Gentianales
Family: Apocynaceae
Genus: Tabernanthe
Species: *T. iboga*

Binomial name Tabernanthe iboga

Iboga (Tabernanthe iboga), also known as *Black bugbane*, is a perennial rainforest shrub and hallucinogen, native to western Africa. Iboga stimulates the central nervous system when taken in small doses and induces visions in larger doses.

Normally growing to a height of 2 m, T. iboga may eventually grow into a small tree up to 10 m tall, given the right conditions. It has small green leaves. Its flowers are white and pink, while the elongated, oval-shaped fruit are orange. Its yellow-coloured roots contains a number of indole alkaloids, most notably ibogaine, which is found in the highest concentration in the root-bark. The root material, bitter in taste, causes an anaesthetic sensation in the mouth as well as systemic numbness to the skin.

Traditional use

The Iboga tree is the central pillar of the Bwiti religion practiced in West-Central Africa, mainly Gabon, Cameroon and the Republic of the Congo, which utilises the alkaloid-containing roots of the plant in a number of ceremonies. Iboga is taken in massive doses by initiates when entering the religion, and on a more regular basis is eaten in smaller doses in connection with rituals and tribal dances, which is usually performed at night time. Bwitists have been subject to persecution by Catholic missionaries, who to this day are thoroughly opposed to the growing religious movement of Bwiti. Léon M'ba, before becoming the first President of Gabon in 1960, defended the Bwiti religion and the use of iboga in French colonial courts. On June 6, 2000, the Council of Ministers of the Republic of Gabon declared Tabernanthe iboga to be a national treasure.

The links and references section of this article provide excellent resource material in articles by Barabe, Goutarel et al. and Samorini.

Addiction treatment

Outside Africa, iboga extracts as well as the purified alkaloid ibogaine are used in treating opiate addiction. The therapy may last several days and upon completion the subject is generally no longer physically dependent. One methadone patient said in the Dutch behind-the-news show 2 vandaag that in just four days he reached a state that normally would have taken him three months, but without the agony. Evidence suggests that ibogaine may also help to interrupt addiction to alcohol and nicotine. The pharmacological effects are rather undisputed with hundreds of peer reviewed papers in support but formal clinical studies have not been completed.

Legal status

Iboga is outlawed or restricted in the U.S., Belgium, Sweden, Switzerland and Denmark. Root material and extracts thereof is obtainable through various European smart shops.

Quotations

- "The Catholic church is a beautiful theory for Sunday, the iboga on the contrary is the practice of everyday living. In church, they speak of God, with iboga, you live God" (Nengue Me Ndjoung Isidore, ecumenical Bwitist religious leader)

Incapacitating agents

The term *incapacitating agent* is defined by the U.S. Department of Defense as "An agent that produces temporary physiological or mental effects, or both, which will render individuals incapable of concerted effort in the performance of their assigned duties."

Incapacitating agents are not primarily intended to kill, but supposedly nonlethal incapacitating agents can kill many of those exposed to them.

The term "incapacitation," when used in a general sense, is roughly equivalent to the term "disability" as used in occupational medicine and denotes the inability to perform a task because of a quantifiable physical or mental impairment. In this sense, any of the chemical warfare agents may incapacitate a victim; however, again by the military definition of this type of agent, incapacitation refers to impairments that are temporary and nonlethal. Thus, riot-control agents are incapacitating because they cause temporary loss of vision due to blepharospasm, but they are not considered military incapacitants because the loss of vision does not last long. Although incapacitation may result from physiological changes such as mucous membrane irritation, diarrhea, or hyperthermia, the term "incapacitating agent" as militarily defined refers to a compound that produces temporary and nonlethal impairment of military performance by virtue of its psychobehavioral or CNS effects.

History

The use of chemicals to induce altered states of mind dates to antiquity and includes the use of plants such as thornapple (Datura stramonium) that contain combinations of anticholinergic alkaloids. The use of nonlethal chemicals to render an enemy force incapable of fighting dates back to at least 600 B.C when Solon's soldiers threw hellebore roots into streams supplying water to enemy troops, who then developed diarrhea. In 184 B.C., Hannibal's army used belladonna plants to induce disorientation, and the Bishop of Münster in A.D. 1672 attempted to use belladonna-containing grenades in an assault on the city of Groningen. In 1881, members of a railway surveying expedition crossing Tuareg territory in North Africa ate dried dates that tribesmen had apparently deliberately contaminated with Hyoscyamus falezlez. In 1908, 200 French soldiers in Hanoi became delirious and experienced hallucinations after being poisoned with a related plant. More recently, accusations of Soviet use of incapacitating agents internally and in Afghanistan were never substantiated. (Although see the Moscow theatre siege case, below).

Following World War II, the United States military investigated a wide range of possible nonlethal, psychobehavioral, chemical incapacitating agents to include psychedelic indoles such as lysergic acid diethylamide (LSD-25) and marijuana derivatives, certain tranquilizers,

as well as several glycolate anticholinergics. One of the anticholinergic compounds, 3-quinuclidinyl benzilate, was assigned the NATO code BZ and was weaponized beginning in the 1960s for possible battlefield use. Although BZ figured prominently in the plot of the 1990 movie, Jacob's Ladder, as the compound responsible for hallucinations and violent deaths in a fictitious American battalion in Vietnam, this agent never saw operational use. Destruction of American stockpiles began in 1988 and is now complete.

Substances known to have been weaponized as incapacitating agents:

- BZ / Agent 15
- LSD
    - Kolokol-1

Documented use of incapacitating agents

There is one documented case of incapacitating agents being used in recent years. In 2002, Chechen terrorists took a large number of hostages in the Moscow theatre siege, and threatened to blow up the entire theatre if any attempt was made to break the siege. An incapacitating agent was used to disable the terrorists whilst the theatre was stormed by special forces. However, the incapacitating agent, unknown at that time, caused many of the hostages to die. The situation was not helped by the fact that the authorities kept the nature of the incapacitating agent secret from doctors trying to treat its victims. At the time, the gas was reported to be an unknown incapacitating agent called "Kolokol-1". The Russian Health Minister Yuri Shevchenko later stated that the incapacitating agent used in the storming of the Moscow theatre siege was a fentanyl derivative.

Psychedelics

Psychedelic drugs are psychoactive drugs whose primary action is to alter the thought processes of the brain. The term is derived from Greek ÈÅÇ· (psyche, "mind") and ´·»µ¹½ (delein, "to manifest"), or ´·»¿Â (delos, "beautiful").

Many psychedelic drugs are thought to disable filters which block or suppress signals related to everyday functions from reaching the conscious mind. These signals are presumed to originate in several other functions of the brain, including but not limited to the senses, emotions, memories and the unconscious (or subconscious) mind. This effect is sometimes referred to as mind expanding, or consciousness expanding as your conscious mind becomes aware of (or sometimes assaulted by) things normally inaccessible to it. At high levels this can overwhelm the sense of self and can result in a dissociative state.

The best definition of what is considered a classic or true psychedelic is the following -- “a psychedelic drug is one which, without causing physical addiction, craving, major physiological disturbances, delirium, disorientation, or amnesia, more or less reliably produces thought, mood, and perceptual changes otherwise rarely experienced except in

dreams, contemplative and religious exaltation, flashes of vivid involuntary memory and acute psychoses". [1] Over the decades, the term has been contaminated to include far more substances than originally intended. Many pharmacologists define psychedelic drugs as chemicals which have an LSD or mescaline like action on certain serotonin receptors. This essentially means tryptamines and phenethylamines, as no psychedelics from other chemical families have been discovered, with the possible exception of piperazines. Many people have applied the term psychedelic to other drugs including cannabis, dissociative arylcyclohexylamines such as PCP and ketamine, tropane deliriants such as atropine, other psychoactives such as Amanita muscaria and Salvia divinorum. More properly, these should be grouped with psychedelics under the category of entheogens, a term which describes the way a drug is used rather than its pharmacological properties.

Psychedelics have a long history of traditional use in native medicine and religion, where they are prized for their perceived ability to promote physical and mental healing. Native American practitioners using peyote have reported success against alcoholism, and Mazatec practitioners routinely use psilocybin mushrooms for divination and healing. Ayahuasca, a psychotropic drug, was used in Peru for religious festivals [Posner, 2006] Link: http://www.walrusmagazine.com/u/register/?ref=anthropology-plants-with-soul

Classic psychedelics include LSD, psilocybin (one active principle of 'magic mushrooms'), mescaline (one active principle of peyote and the San Pedro cactus), LSA (morning glory seeds) and also Ayahuasca (known in Beatnik literature as yajé), a traditional shamanic tea brewed from plants containing dimethyltryptamine and harmine or harmaline. Some newer synthetics such as MDMA (ecstasy), 2C-B (nexus), DOM (STP) and 5-MeO-DIPT (Foxy Methoxy) have also enjoyed some popularity.

Pharmacological classes of psychedelics, and their general subjective effects

Serotonergic psychedelics (serotonin 5-HT2A receptor agonists)

This class of psychedelics includes the major hallucinogens, including tryptamine-based compounds like LSD and psilocybin, and phenethylamine-based compounds like mescaline and 2C-B. Many of the tryptamines and phenethylamines cause remarkably similar effects, despite their different chemical structure. However, most users report that the two families have subjectively different qualities in the "feel" of the experience which are difficult to describe. At lower doses, these include sensory distortions such as the warping of surfaces, shape suggestibility, and color variations. Users often report intense colors that they have not previously experienced, and repetitive geometric shapes are common. Higher doses often cause intense and fundamental distortions of sensory perception such as synesthesia or the experience of additional spatial, temporal, or time dimensions. Some compounds, such as 2C-B, have extremely tight "dose curves," meaning the difference between a non-event and an overwhelming disconnection from reality can be very slight. There can be very real differences, however, such as 5-MeO-DMT which rarely produces the visual effects typical of other psychedelics. Some drugs, such as the ß-carbolines, produce very different effects from the more standard types of psychedelics.

Empathogens and/or entactogens (serotonin releasers)

The empathogens are phenethylamines such as MDMA, MDA, and similar drugs, the effects of which are characterized by feelings of openness, euphoria, empathy, love, and heightened self-awareness, but not by visual hallucinations. Their initial adoption by the dance club sub-culture is probably due to the enhancement of the overall social and musical experience.

Cannabinoids (CB-1 cannabinoid receptor agonists)

The cannabinoids are Tetrahydrocannabinol (THC) and related compounds, which are capable of activating the bodies endogenous cannabanoid system. Some effects may include: general change in consciousness, mild euphoria, feelings of general well-being, relaxation or stress reduction, increased appreciation of humor, music and other art, joviality, metacognition and introspection, enhanced recollection of episodic memory, increased sensuality, loss of inhibition, increased awareness of sensation, creative or philosophical thinking, disruption of linear memory, paranoia, agitation, and anxiety, potentiation of other psychedelics, increased awareness of patterns and color.

Other (psychedelic activity questioned)

The effects of myristicin and elemicin (found in nutmeg) are reported are similar to that of cannabis, more so of the cannabidiol component rather than THC, but with a much longer duration, slow onset, and undesirable side effects.

Cryogenine (Vertine) is the active constituent of sinicuichi. Although vertine has anticholinergic properties, use of sinicuichi tends to produce psychedelic effects rather than that of a deliriant (this could possibly be dose related). The primary noted effects include auditory distortions, improved memory and relaxation.

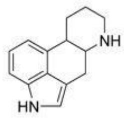
See also

- Entheogen
- Psychedelic
- Psychedelics, dissociatives and deliriants
- Psychoactive drug
- Dissociative drug

References

1. ^ L. Grinspoon, J. Bakalar (1979), Psychedelic Drugs Reconsidered. p. 9. ISBN 0-9641568-5-7

Lysergamides

 Chemical structure of ergoline

Ergoline is a chemical compound whose structural skeleton is contained in a diverse range of alkaloids and a few psychedelic drugs (ololiuhqui, LSD). Substances derived from ergoline are used clinically for the purpose of vasoconstriction (5-HT 1 Agonists - Ergotamine) and in the treatment of migraine (used with caffeine) and Parkinson's disease, some are implicated in the disease ergotism. Ergometrine and ergotamine are listed as Table I precursors under the United Nations Convention Against Illicit Traffic in Narcotic Drugs and Psychotropic Substances[1] .

Chemistry

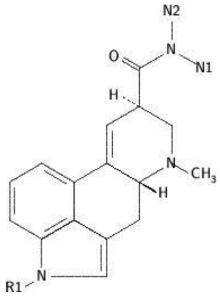
There are three main classes of ergoline derivatives, the water-soluble amides of *lysergic acid*, the water-insoluble *ergopeptide* alkaloids, and the *clavine* group.

Lysergic acid amides

- Ergine (d-lysergic acid amide, LSA, LAA, LA-111)
  - IUPAC name: 9,10-didehydro-6-methylergoline-8beta-carboxamide
  - CAS number: 478-94-4
- Ergonovine (ergobasine)
  - INN: ergometrine
  - IUPAC name: (8beta(S))9,10-didehydro-N-(2-hydroxy-1-methylethyl)6-methyl-ergoline-8-carboxamide
  - CAS number: 60-79-7
- Methergine (ME-277)
  - INN: methylergometrine
  - IUPAC name: (8beta(S))9,10-didehydro-N-(1-(hydroxymethyl)propyl)6-methyl-ergoline-8-carboxamide
  - CAS number: 113-42-8
- Methysergide (UML-491)
  - INN: methysergide
  - IUPAC name: (8beta)9,10-didehydro-N-(1-(hydroxymethyl)propyl)1,6-dimethyl-ergoline-8-carboxamide
  - CAS number: 361-37-5
- LSD (D-lysergic acid diethylamide, LSD-25)
  - INN: lysergide

- IUPAC name: (8beta)9,10-didehydro-N,N-diethyl-6-methyl-ergoline-8-carboxamide
- CAS number: 50-37-3

The relationship between these compounds is summarized in the following structural formula and table of substitutions.



Name	R1	N1	N2
Ergine			
Ergonovine		$CH(CH_3)CH_2OH$	
Methergine		$CH(CH_2CH_3)CH_2OH$	
Methysergide	CH_3	$CH(CH_2CH_3)CH_2OH$	
LSD		CH_2CH_3	CH_2CH_3

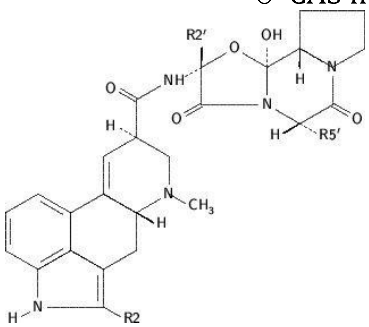
Peptide alkaloids

These compounds have a tripeptide structure attached to the basic ergoline ring, in the same location as the amide group of the lysergic acid derivatives. This tripeptide moiety contains an unusual cyclol bond >N-C(OH)< at the juncture between the two lactam rings. Some of the important *ergopeptides* are summarized below. In addition to the following ergopeptides, a commonly encountered term is *ergotoxine*, which refers to a mixture of equal proportions of ergocristine, ergocornine and ergocryptine.

- Ergotamine
  - IUPAC name: Ergotaman-3',6',18-trione, 12'-hydroxy-2'-methyl-5'-(phenylmethyl)-, (5'-alpha)- (9CI)
  - CAS number: 113-15-5
- Ergocristine
  - IUPAC name: Ergotaman-3',6',18-trione, 12'-hydroxy-2'-(1-methylethyl)5'-(phenylmethyl)-, (5'-alpha)-
  - CAS number: 511-08-0
- Ergocornine
  - IUPAC name: Ergotaman-3',6',18-trione, 12'-hydroxy-2',5'-bis(1-methylethyl)-, (5'-alpha)-
  - CAS number: 564-36-3
- Ergocryptine

- IUPAC name:Ergotaman-3',6',18-trione, 12'-hydroxy-2'-(1-methylethyl)5'-(2-methylpropyl)-, (5'alpha)- (9CI)
- CAS number: 511-09-1

- Bromocriptine (INN)
  - IUPAC name: Ergotaman-3',6',18-trione, 2-bromo-12'-hydroxy-2'-(1-methylethyl)5'-(2-methylpropyl)-, (5'alpha)-
  - CAS number: 25614-03-3
- Ergovaline
  - IUPAC name: Ergotaman-3',6',18-trione, 12'-hydroxy-2'-methyl-5'-(1-methylethyl)-, (5'alpha)-
  - CAS number: 2873-38-3



Name	R2	R2'	R5'
Ergotamine		CH_3	benzyl
Ergocristine		$CH(CH_3)_2$	benzyl
Ergocornine		$CH(CH_3)_2$	$CH(CH_3)_2$
Ergocryptine		$CH(CH_3)_2$	$CH_2CH(CH_3)_2$
Bromocriptine	Br	$CH(CH_3)_2$	$CH_2CH(CH_3)_2$
Ergovaline		CH_3	$CH(CH_3)_2$

Clavines

A variety of modifications to the basic ergoline are seen in nature, for example *agroclavine*, *elymoclavine*, *lysergol*. Those deriving from *dimethylergoline* are referred to as *clavines*.

Others

Some synthetic ergoline derivatives do fall easily into any of the above groups. Some examples are:

- Pergolide (INN)
  - IUPAC name: (8beta)8-((methylthio)methyl)6-propyl-ergoline
  - CAS number: 66104-22-1
- Lisuride (INN)
  - IUPAC name: 3-(9,10-didehydro-6-methylergolin-8alpha-yl)1,1-diethylurea
  - CAS number: 18016-80-3

History & Uses

Ergoline alkaloids were first isolated from ergot, a fungus that infects grain and causes the disease ergotism. Ergot also has a long history of medicinal use, which led to attempts to characterize its activity chemically. This began in 1907 with the isolation by G. Barger and F. H. Carrin of ergotoxine, so-named since it appeared to exhibit more of the toxicity of ergot than its therapeutic qualities. With the isolation of *ergotamine* in 1918 by A. Stoll came the first therapeutic use of isolated ergoline alkaloids.

With the determination of the basic chemical structure of the ergot alkaloids in the early 1930s, an era of intensive exploration of synthetic derivatives began. In addition to the naturally occurring *ergonovine* (used as an oxytocic) and *ergotamine* (an analgesic used to control migraine), synthetic derivatives of continuing importance today are the oxytocic *methergine*, the anti-migraine drugs *dihydroergotamine* and *methysergide*, the anti-senility nootropic (smart drug) *Hydergine*™ (a mixture of dihydroergotoxine mesylates, INN: ergoline mesylates), and *bromocriptine*, used for numerous purposes including treatment of Parkinson's disease. Newer synthetic ergolines used for Parkinson's disease include *pergolide* and *lisuride*. Perhaps the most famous ergoline derivative of all is the psychedelic drug LSD.

In 1960, Albert Hofmann (discoverer of methergine, dihydroergotamine, Hydergine and LSD) delivered a speech that was to cause shockwaves of incredulity and even disbelief in the scientific community. Ergoline alkaloids, previously only known from the lower fungi, had been found in two species of flowering plants. These were the Mexican species Rivea corymbosa and Ipomoea violacea of the Convolvulaceae (morning glory) family, the seeds of which were identified as the psychedelic plant drugs known as "ololiuhqui" and "tlitliltzin". Hofmann's result was later confirmed by other studies. The principal alkaloids in the seeds are ergine and its optical isomer isoergine, with several other lysergic acid derivatives and clavines present in lesser amounts. The Hawaiian species Argyreia nervosa was later found to include similar alkaloids. It is possible, though not proven, that ergine and/or isoergine are responsible for the hallucinogenic effects.

Ergotamine tartrate, the salt form of Ergoline, is marketed under the trade name Avetol.

See also

- Ergot

- LSD

References

1. ^ http://www.incb.org/pdf/e/list/red.pdf

LSD

Systematic (IUPAC) name

(6aR,9R)-N,N-Diethyl-7-methyl-4,6,6a,7,8,9-hexahydroindolo-[4,3-fg]quinoline-9-carboxamide

Identifiers

CAS number 50-37-3

PubChem 5761

Chemical data

Formula $C_{20}H_{25}N_{3}O$

Mol. weight 323.43 g/mol

SMILES
O=[C@@](N(CC)CC)[C@H]
1CN(C)[C@](C2=C1)([H])
CC3=CNC4=C3C2=CC=C4

Synonyms LSD, LSD-25, lysergide, d-lysergic acid diethylamide

Physical data

Melt. point 80 °C (176 °F)

Pharmacokinetic data

Metabolism hepatic

Half life 3 hours

Excretion renal

Therapeutic considerations

Pregnancy cat. X

Legal status Schedule III(CA) Schedule I(US)

Routes Oral, Intravenous, Transdermal

Lysergic acid diethylamide, commonly called *LSD*, *acid*, or *LSD-25*, is a semisynthetic psychedelic drug. The short form LSD comes from the German "*L*ysergs*ä*ure-*d*iethylamid". A typical single dose of LSD is between 100 and 500 micrograms, an amount roughly equal to one-tenth the mass of a grain of sand. Threshold effects can be felt with as little as 20 micrograms[1] but most users may prefer to take larger doses.[2]

The effects of LSD can vary greatly depending on factors such as previous experiences, state of mind and environment, as well as dose strength. Generally, LSD causes expansion and altered experience of senses, emotions, memories, time, and awareness for 8 to 14 hours. In addition, LSD may produce visual effects such as moving geometric patterns, "trails" behind moving objects, and brilliant colors. LSD does not produce hallucinations in the strict sense but instead illusions and vivid daydream-like fantasies, in which ordinary objects and experiences can take on entirely different appearances or meanings. At higher doses it can cause synesthesia. Some users cite the LSD experience as causing long-term or permanent changes in their personality and life perspective.

LSD is synthesized from lysergic acid derived from ergot, a grain fungus that typically grows on rye. LSD is sensitive to oxygen, ultraviolet light, and chlorine, especially in solution (though its potency may last years if the substance is stored away from light and moisture at low temperature). In pure form it is colorless, odorless, and mildly bitter. LSD is typically delivered orally, usually on a substrate such as absorbent blotter paper, a sugar cube, or gelatin. In its liquid form, it can be administered by intramuscular or intravenous injection, or even in the form of eye-drops

Introduced by Sandoz Laboratories as a drug with various psychiatric uses, LSD quickly became a therapeutic agent that appeared to show great promise. However, the extra-medical use of the drug in Western society in the middle years of the twentieth century led to a political firestorm that resulted in the banning of the substance for medical as well as recreational and spiritual uses. Despite this, it is still considered a promising drug in some intellectual circles, and organizations such as MAPS, Heffter Research Institute and the Albert Hofmann Foundation exist to fund, encourage and coordinate research into its medical uses.

Origins and history

LSD was first synthesized in 1938 by Swiss chemist Dr. Albert Hofmann at the Sandoz Laboratories in Basel, Switzerland, as part of a large research program searching for medically useful ergot alkaloid derivatives. Its psychedelic properties were unknown until 5 years later, when Hofmann, acting on what he has called a "peculiar presentiment," returned to work on the chemical. He attributed the discovery of the compound's psychoactive effects to the accidental absorption of a tiny amount through his skin on April 16, which led to him testing a larger amount (250 µg) on himself for psychoactivity.[3]

Until 1966, LSD and psilocybin were provided by Sandoz Laboratories free of charge to interested scientists under the trade name "Delysid".[3] The use of these compounds by psychiatrists to gain a better subjective understanding of the schizophrenic experience was an accepted practice. Many clinical trials were conducted on the potential use of LSD in psychedelic psychotherapy, generally with very positive results.

Cold War era intelligence services were keenly interested in the possibilities of using LSD for interrogation and mind control, and also for large-scale social engineering. The CIA conducted extensive research on LSD, which was mostly destroyed.[4] LSD was a central research area for Project MKULTRA, the code name for a CIA mind-control research program begun in the 1950s and continued until the late 1960s. Tests were also conducted by the U.S. Army Biomedical Laboratory (now known as the U.S. Army Medical Research Institute of Chemical Defense) located in the Edgewood Arsenal at Aberdeen Proving Grounds. Volunteers would take LSD and then perform a battery of tests to investigate the effects of the drug on soldiers. Based on remaining publicly available records, the projects seem to have concluded that LSD was of little practical use as a mind control drug and moved on to other drugs. Both the CIA and the Army experiments became highly controversial when they became public knowledge in the 1970s, as the test subjects were not normally informed of the nature of the experiments, or even that they were subjects in experiments at all. Several subjects developed severe mental illnesses and even committed suicide after the experiments. The controversy led to President Ford's creation of the Rockefeller Commission and new regulations on informed consent.

The British government also engaged in LSD testing; in 1953 and 1954, scientists working for MI6 dosed servicemen in an effort to find a "truth drug". The test subjects were not informed that they were being given LSD, and had in fact been told that they were participating in a medical project to find a cure for the common cold. One subject, aged 19 at the time, reported seeing "walls melting, cracks appearing in people's faces … eyes would run down cheeks, Salvador Dalí-type faces … a flower would turn into a slug". After keeping the trials secret for many years, MI6 agreed in 2006 to pay the former test subjects financial compensation. Like the CIA, MI6 decided that LSD was not a practical drug for brainwashing purposes.[5]

LSD first became popular recreationally among a small group of mental health professionals such as psychiatrists and psychologists during the 1950s, as well as by socially prominent and politically powerful individuals such as Henry and Clare Boothe Luce to whom the early LSD researchers were connected socially.

Several mental health professionals involved in LSD research, most notably Harvard psychology professors Drs. Timothy Leary and Richard Alpert, became convinced of LSD's potential as a tool for spiritual growth. In 1961, Dr. Timothy Leary received grant money from Harvard University to study the effects of LSD on test subjects. 3,500 doses were given to over 400 people. Of those tested, 90% said they would like to repeat the experience, 83% said they had "learned something or had insight," and 62% said it had changed their life for the better.

Their research became more esoteric and controversial, as Leary and Alpert alleged links between the LSD experience and the state of enlightenment sought after in many mystical traditions. They were dismissed from the traditional academic psychology community, and as such cut off from legal scientific acquisition of the drug. Drs. Leary and Alpert somehow

acquired a quantity of LSD and relocated to a private mansion, where they continued their research. The experiments lost their scientific character as the pair evolved into countercultural spiritual gurus associated with the hippie movement, encouraging people to question authority and challenge the status quo, a concept summarized in Leary's catchphrase, "Turn on, tune in, drop out".

The drug was banned in the United States in 1967, with scientific therapeutic research as well as individual research also becoming prohibitively difficult. Many other countries, under pressure from the U.S., quickly followed suit. Since 1967, underground recreational and therapeutic LSD use has continued in many countries, supported by a black market and popular demand for the drug. Legal, academic research experiments on the effects and mechanisms of LSD are also conducted on occasion, but rarely involve human subjects. Despite its proscription, the hippie counterculture continued to promote the regular use of LSD, led by figures such as Leary and psychedelic rock bands such as The Grateful Dead.

According to Leigh Henderson and William Glass, two researchers associated with the NIDA who performed a 1994 review of the literature, LSD use is relatively uncommon when compared to the abuse of alcohol, marijuana, cocaine and prescription drugs. Over the previous fifteen years, long-term usage trends stayed fairly stable, with roughly 5% of the population using the drug and most users being in the 16 to 23 age range. Henderson and Glass found that LSD users typically partook of the substance on an infrequent, episodic basis, then "maturing out" after two to four years. Overall, LSD appeared to have comparatively few adverse health consequences, of which "bad trips" were the most commonly reported (and, the researchers found, one of the chief reasons youths stop using the drug).[6]

Dosage

LSD is, by mass, one of the most potent drugs yet discovered. Both subjective reports and pharmacological methods such as receptor binding assays determine LSD to be, per mole, around 100 times more potent than psilocybin and psilocin and around 4,000 times more potent than mescaline. Dosages of LSD are measured in micrograms (µg), or millionths of a gram. By comparison, dosages of almost all other drugs, both recreational and medical, are measured in milligrams (mg), or thousandths of a gram.

The dosage level that will produce a threshold hallucinogenic effect in humans is generally considered to be 20–30 ¼g, with the drug's effects becoming markedly more evident at higher dosages.[7][1] According to Glass and Henderson's review, black-market LSD is largely unadulterated though sometimes contaminated by manufacturing by-products. Typical doses in the 1960s ranged from 200 to 1000 µg, while street samples of the 1970s contained 30 to 300 µg. By the mid-1980s, the average had reduced to about 100 to 125 µg, lowering still further in the 1990s to the 20–80 µg range. (Lower doses, Glass and Henderson found, generally produce fewer bad trips.)[6] Dosages by frequent users can be as high as 1,200 µg (1.2 mg), although such a high dosage may precipitate unpleasant physical and psychological reactions.

Estimates for the lethal dosage (LD***50***) of LSD range from 200 ¼g/kg to more than 1 mg/kg of human body mass, though most sources report that there are no known human cases of such an overdose. Other sources note one report of a suspected fatal overdose of

LSD in which there were indications that ~1/3 of a gram (320 mg or 320,000 μg) had been injected intravenously, i.e., over 3,000 more typical oral doses of ~100 μg had been injected.[8]

LSD is not considered addictive, in that its users do not exhibit the medical community's commonly accepted definitions of addiction and physical dependence. Rapid tolerance build-up prevents regular use, and there is cross-tolerance shown between LSD, mescaline and psilocybin. This tolerance diminishes after a few days' abstention from use. As with any psychotropic substance there is a risk of psychological dependence; however, as with most psychedelics, this risk is relatively low .

Effects

Pharmacodynamical

LSD's secondary effects normally last from fifty-two to seventy-five hours,[2] though as Sandoz's prospectus for "Delysid" warned, "intermittent disturbances of affect may occasionally persist for several days."[3] Contrary to early reports and common belief, LSD effects do not last longer than significant levels of the drug in the blood. Aghajanian and Bing[9] found LSD had an elimination half-life of 175 minutes, while, more recently, Papac and Foltz[10] reported that 1 μg/kg oral LSD given to a single male volunteer had an apparent plasma half-life of 5.1 hours, with a peak plasma concentration of 1.9 ng/mL at 3 hours post-dose. Notably, Aghajanian and Bing found that blood concentrations of LSD matched the time course of volunteers' difficulties with simple arithmetic problems.

Some reports indicate that administration of chlorpromazine (Thorazine) or similar typical antipsychotic tranquilizers will not end an LSD trip, but rather will just immobilize and numb the patient.[11] While it also may not end an LSD trip, the best chemical treatment for a "bad trip" is an anxiolytic agent such as diazepam (Valium) or another benzodiazepine. Some have suggested that administration of niacin (nicotinic acid, vitamin B3) could be useful to end the LSD user's experience of a "bad trip".[12] The nicotinic acid in niacin as opposed to niacinamide, will produce a full body heat rash, due to widening of peripheral blood vessels. The effect is somewhat akin to a poison ivy rash. Although it is not clear to what extent the effects of LSD are reduced by this intervention, the physical effect of an itchy skin rash may itself tend to distract the user from feelings of anxiety. The rash itself is temporary and disappears within a few hours. It is not clear how effective this method would be for people having serious adverse psychological reactions.

LSD affects a large number of the G protein coupled receptors, including all dopamine receptor subtypes, all adrenoreceptor subtypes as well as many others. LSD binds to most serotonin receptor subtypes except for 5-HT3 and 5-HT4. However, most of these receptors are affected at too low affinity to be activated by the brain concentration of approximate 10–20 nM.[13] Recreational doses of LSD can affect 5-HT1A, 5-HT2A, 5-HT2C, 5-HT5A, 5-HT5 B and 5-HT6 The hallucinogenic effects of LSD are attributed to its strong partial agonist effects at 5-HT2A receptors as specific 5-HT2A agonist drugs are hallucinogenic and largely 5-HT2A specific antagonists block the hallucinogenic activity of LSD.[13] Exactly how this produces the drug's effects is unknown, but it is thought that it works by increasing glutamate release

and hence excitation in the cortex, specifically in layers IV and V.[14] In the later stages, LSD acts through DARPP-32 - related pathways that are likely the same for multiple drugs including cocaine, amphetamine, nicotine, caffeine, PCP, ethanol and morphine.[15] A particularly compelling look at the actions of LSD was performed by Barry Jacobs recording from electrodes implanted into cat raphe nuclei.[16] Behaviorally relevant doses of LSD result in a complete blockade of action potential activity in the dorsal raphe, effectively shutting off the principal endogenous source of serotonin to the telencephalon.

Physical

Physical reactions to LSD are highly variable and may include the following: uterine contractions, hyperthermia (body temperature increase), elevated blood sugar levels, dry-mouth, goose bumps, heart-rate increase, jaw clenching, nausea, perspiration, pupil-dilation, salivation, mucus production, sleeplessness, paresthesia, euphoria or dysphoria, hyperreflexia, tremors and synesthesia. Cramps and muscle tension or soreness are also commonly reported, and this may be a result of the drug's effect on soft tissues such as the uterus

LSD was studied in the 1960s by Eric Kast as a painkiller for serious and chronic pain caused by cancer or other major trauma.[17] Even at low (sub-psychedelic) dosages, it was found to be at least as effective as traditional opiates while being much longer lasting (pain reduction lasting as long as a week after peak effects had subsided). Kast attributed this effect to a decrease in anxiety. This reported effect is being tested (though not using LSD) in an ongoing (as of 2006) study of the effects of the hallucinogen psilocybin on anxiety in terminal cancer patients.

Furthermore, LSD has been illicitly used as a treatment for cluster headaches, an uncommon but extremely painful disorder. Researcher Peter Goadsby describes the headaches as "worse than natural childbirth or even amputation without anesthetic."[18] Although the phenomenon has not been formally investigated, case reports indicate that LSD and psilocybin can reduce cluster pain and also interrupt the cluster-headache cycle, preventing future headaches from occurring. Currently existing treatments include various ergolines, among other chemicals, so LSD's efficacy may not be surprising. A dose-response study, testing the effectiveness of both LSD and psilocybin is, as of 2006, being planned at McLean Hospital. A 2006 study by McLean researchers interviewed 53 cluster-headache sufferers who treated themselves with either LSD or psilocybin, finding that a majority of the users of either drug reported beneficial effects.[19] Unlike attempts to use LSD or MDMA in psychotherapy, this research involves non-psychological effects and often sub-psychedelic dosages; therefore, it is plausible that a respected medical use of LSD will arise.[20]

Psychological

LSD's psychological effects (colloquially called a "trip") vary greatly from person to person, from one trip to another, and even as time passes during a single trip. Widely different effects emerge based on what Leary called set and setting; the "set" being the

general mindset of the user, and the "setting" being the physical and social environment in which the drug's effects are experienced.

An LSD trip can have long lasting or even permanent neutral, negative, and positive psychoemotional effects. LSD experiences can range from indescribably ecstatic to extraordinarily difficult; many difficult experiences (or "bad trips") result from a panicked user feeling that he or she has been permanently severed from reality and his or her ego. If the user is in a hostile or otherwise unsettling environment, or is not mentally prepared for the powerful distortions in perception and thought that the drug causes, effects are more likely to be unpleasant.

Conversely, a comfortable environment and a relaxed, balanced and open mindset will often result in a pleasant experience.

Many users experience a dissolution between themselves and the "outside world": cognitive differences between subject ("I") and object ("me", "you", "it") break down or seem absurd.[21] This unitive quality may play a role in the spiritual and religious aspects of LSD.

Some experts hypothesize that drugs such as LSD may be useful in psychotherapy, especially when the patient is unable to "unblock" repressed subconscious material through other psychetherapeutic methods,[22] and also for treating alcoholism. One study concluded, "The root of the therapeutic value of the LSD experience is its potential for producing self-acceptance and self-surrender,"[23] presumably by forcing the user to face issues and problems in that individual's psyche. Many believe that, in contrast, other drugs (such as alcohol, heroin, and cocaine) are used to escape from reality. Studies in the 1950s that used LSD to treat alcoholism professed a 50% success rate,[24] higher than estimates near 10% for Alcoholics Anonymous.[25] Some LSD studies were criticized for methodological flaws, and different groups had inconsistent results. Mangini's 1998 paper reviews this history and concludes that the efficacy of LSD in treating alcoholism remains an open question.[26]

Many notable individuals have commented publicly on their experiences with LSD. Some of these comments date from the era when it was legally available in the US and Europe for non-medical uses, and others pertain to psychiatric treatment in the 1950s and 60s. Still others describe experiences with illegal LSD, obtained for philosophic, artistic, therapeutic, spiritual, or recreational purposes.

Sensory/perception

Generally beginning within thirty to ninety minutes after ingestion and continuing for the following six to twelve hours, the user may experience anything from subtle changes in perception to overwhelming cognitive shifts.

Changes in aural and visual perception are common, ranging from mild to profound.[21][27] These sensory changes include basic "high-level" distortions such as the appearance of moving geometric patterns, new textures on objects, blurred vision, image trailing, shape suggestibility and color variations. Inanimate objects are frequently described as "breathing". Users sometimes describe experiencing new, previously-unseen colors; sights and sounds may take on greater intensity or have more of an impact. Users commonly report that the inanimate world appears to animate in an unexplained way; that is, objects

that are static in three dimensions can seem to be moving relative to one or more additional spatial dimensions.[28]

Higher doses often bring about shifts at a lower cognitive level, causing an intense and fundamental reinterpretation of sensory perception, symptomatic of synesthesia.

Spiritual

LSD is considered an entheogen because it often catalyzes intense spiritual experiences where users feel they have come into contact with a greater spiritual or cosmic order. It is common for users to achieve insights into the way the mind works and some users experience permanent or long-lasting changes in their life perspective. Some users consider LSD a religious sacrament, or a powerful tool for access to the divine. Many books have been written comparing the LSD trip to the state of enlightenment of eastern philosophy.

Such experiences under the influence of LSD have been observed and documented by researchers such as Timothy Leary and Stanislav Grof. For example, Walter Pahnke conducted the Good Friday Marsh Chapel Experiment under Leary's supervision, performing a double blind experiment on the administration of psilocybin to volunteers who were students in religious graduate programs, e.g., divinity or theology.[29] That study showed that hallucinogens could reliably be used to induce mystical religious states (at least in people with a spiritual predisposition).

Physical dangers

Although LSD is generally considered nontoxic, it may temporarily impair the ability to make sensible judgments and understand common dangers, thus making the user susceptible to accidents and personal injury.

There is also some indication that LSD may trigger a dissociative fugue state in individuals who are taking certain classes of antidepressants such as lithium salts and tricyclics. In such a state, the user has an impulse to wander, and may not be aware of his or her actions, which can lead to physical injury.[30] SSRIs are believed to interact more benignly, with a tendency to noticeably reduce LSD's subjective effects.[31] Similar and perhaps greater reductions have also been reported with MAOIs.[30]

As Albert Hofmann reports in LSD – My Problem Child, the early pharmacological testing Sandoz performed on the compound (before he ever discovered its psychoactive properties) indicated that LSD has a pronounced effect upon the mammalian uterus. Sandoz testing showed that LSD can stimulate uterine contractions with efficacy comparable to ergobasine, the active uterotonic component of the ergot fungus (Hofmann's work on ergot derivatives also produced a modified form of ergobasine which became a widely accepted medication used in obstetrics, under the trade name Methergine). LSD use by pregnant women is therefore contraindicated.[3]

Initial studies in the 1960s and 70s raised concerns that LSD might produce genetic damage or developmental abnormalities in fetuses. However, these initial reports were based on in vitro studies or were poorly controlled and have not been substantiated. In studies of chromosomal changes in human users and in monkeys, the balance of evidence

suggests no significant increase in chromosomal damage. For example, studies were conducted with people who had been given LSD in a clinical setting.[32] White blood cells from these people were examined for visible chromosomal abnormalities. Overall, there appeared to be no lasting changes. Several studies have been conducted using illicit LSD users and provide a less clear picture. Interpretation of these data is generally complicated by factors such as the unknown chemical composition of "street" LSD and concurrent use of other psychoactive drugs. It seems possible that the small number of congenital abnormalities reported in users of street LSD is either coincidental or related to factors other than a toxic effect of pure LSD.

Flashbacks and HPPD

There is a reported possibility of "flashbacks", a psychological phenomenon in which an individual experiences an episode of some of the subjective effects of LSD (this may be a positive or negative experience) long after the drug has been consumed and worn off — sometimes weeks, months or even years afterward.

Colloquial usage of the term "flashbacks" refers to any experience reminiscent of LSD effects; these are commonly occasional brief experiences. However, psychiatry recognizes a disorder in which LSD-like effects are persistent and cause clinically-significant impairment or distress. This chronic flashback syndrome is called Hallucinogen Persisting Perception Disorder (HPPD), a DSM-IV diagnosis. Several scientific journal articles have described the disorder.[33]

Several studies have tried to determine how likely a "normal" user (that is a user not suffering from known psychiatric conditions) of LSD is to experience flashbacks. The larger studies include Blumenfeld's in 1971[34] and Naditch and Fenwick's in 1977,[35] which arrived at figures of 20% and 28%, respectively. A recent review suggests that HPPD (according to the DSM-IV definition) caused by LSD appears to be rare and affects a distinctly vulnerable subpopulation of users.[36] Differences in the estimated prevalence of flashbacks may partly depend on the multiple meanings of the term and the fact that hallucinogen persisting perception disorder can only be diagnosed in a person who admits to their health care practitioner that they have used hallucinogens.

Debate continues over the nature and causes of chronic flashbacks. Some say HPPD is a manifestation of post-traumatic stress disorder, not related to the direct action of LSD on brain chemistry, and vary according to the susceptibility of the individual to the disorder. Many emotionally intense experiences can lead to flashbacks when a person is reminded acutely of the original experience. However, not all published case reports of chronic flashbacks appear to describe an anxious hyper-vigilant state reminiscent of post-traumatic stress disorder.

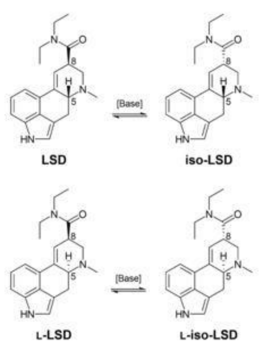
An alternative theory regarding flashbacks postulates that it is a form of perceptual learning. Although unusual perceptual experiences may be just as common among people with no history of having taken the drug, people who have taken LSD may be more likely to associate these otherwise normal psychological events with the experiences they remember having had while on LSD. Under this theory, HPPD would be a separate, more serious, and far less common psychological condition. "Mere" flashbacks, in comparison, may be

experienced by a broad segment of the population, and only attributed to LSD by those who have tried the drug.

Psychosis

There are some cases of LSD inducing or triggering a psychosis in people who were apparently healthy prior to taking LSD. This issue was reviewed extensively in a 1984 publication by Rick Strassman.[37] In most cases, the psychosis-like reaction is of short duration, but in other cases it may be chronic. It is difficult to determine if LSD itself induces these reactions or if it merely triggers latent conditions that would have manifested themselves otherwise. The similarities of time course and outcomes between putatively LSD-precipitated and other psychoses suggests that the two types of syndromes are not different and that LSD may have been a nonspecific trigger. Several studies have tried to estimate the prevalence of LSD-induced prolonged psychosis arriving at numbers of around 4 in 1,000 individuals (0.8 in 1,000 volunteers and 1.8 in 1,000 psychotherapy patients in Cohen 1960;[38] 9 per 1,000 psychotherapy patients in Melleson 1971[39]). But these rates are far lower than the lifetime prevalence for psychotic conditions: schizophrenia, to pick just one type of psychosis, has a lifetime prevalence of about 1% in populations that are not exposed to LSD. In itself, this suggests no causative link between LSD and chronic psychotic disorders.

Chemistry



The four possible isomers of LSD. Only LSD is psychoactive.

LSD is an example of an ergoline derivative. It is commonly produced from lysergic acid, which is made from ergotamine, a substance derived from the ergot fungus on rye, or from ergine (lysergic acid amide), a chemical found in morning glory and hawaiian baby woodrose seeds. It is theoretically possible to manufacture LSD from morning glory or hawaiian baby woodrose seeds although this is not economically feasible, and these seeds have never been found to be a successful starting material for LSD production. Lysergic acid can also be synthesized in the laboratory by relatively complex total syntheses.

LSD is a chiral compound with two stereocenters at the carbon atoms C-5 and C-8, so that theoretically four different optical isomers of LSD could exist. LSD, also called (+)-D-LSD, has the absolute configuration (5R,8R). The C-5 isomers of lysergamides do not exist in nature and are not formed during the synthesis from D-lysergic acid. However, LSD and iso-LSD, the two C-8 isomers, are rapidly interconverting in the presence of base. Non-psychoactive iso-

LSD which has formed during the synthesis can be removed by chromatography and can be isomerized to LSD.

Stability

"LSD," writes the chemist Alexander Shulgin, "is an unusually fragile molecule."[2] It is stable for indefinite amounts of time if stored, as a salt or in water, at low temperature and protected from air and light exposure. Two portions of its molecular structure are particularly sensitive, the carboxamide attachment at the 8-position and the double bond between the 8-position and the aromatic ring. The former is affected by high pH, and if perturbed will produce isolysergic acid diethylamide (iso-LSD), which is biologically inactive. If water or alcohol adds to the double bond (especially in the presence of light), LSD converts to "lumi-LSD", which is totally inactive in human beings, to the best of current knowledge. Furthermore, chlorine destroys LSD molecules on contact; even though chlorinated tap water typically contains only a slight amount of chlorine, because a typical LSD solution only contains an infinitesimal amount of LSD, dissolving LSD in tap water is likely to completely eliminate the substance.[2]

A controlled study was undertaken to determine the stability of LSD in pooled urine samples.[40] The concentrations of LSD in urine samples were followed over time at various temperatures, in different types of storage containers, at various exposures to different wavelengths of light, and at varying pH values. These studies demonstrated no significant loss in LSD concentration at 25 degrees C for up to 4 weeks. After 4 weeks of incubation, a 30% loss in LSD concentration at 37 degrees C and up to a 40% at 45 degrees C were observed. Urine fortified with LSD and stored in amber glass or nontransparent polyethylene containers showed no change in concentration under any light conditions. Stability of LSD in transparent containers under light was dependent on the distance between the light source and the samples, the wavelength of light, exposure time, and the intensity of light. After prolonged exposure to heat in alkaline pH conditions, 10 to 15% of the parent LSD epimerized to iso-LSD. Under acidic conditions, less than 5% of the LSD was converted to iso-LSD. There was also demonstrated that trace amounts of metal ions in buffer or urine could catalyze the decomposition of LSD and that this process can be avoided by the addition of EDTA.

Production

Only a small amount of ergotamine tartrate is required to produce LSD in large batches. For example, 25 kg of ergotamine tartrate can produce 5 or 6 kg of pure LSD crystal that, under ideal circumstances, could be processed into 100 million dosage units, assuming a typical "hit" of 125 ¼g. This is more than enough to meet what is believed to be the entire annual U.S. demand for the drug. LSD manufacturers only need to create a small quantity of the substance, and thus they enjoy an ease of transport and concealment not available to traffickers of other illegal drugs (such as cannabis and cocaine).[41]

Manufacturing LSD requires laboratory equipment and experience in the field of organic chemistry. It takes two or three days to produce 30 to 100 grams of pure compound. It is

believed that LSD usually is not produced in large quantities, but rather in a series of small batches. This technique minimizes the loss of precursor chemicals in case a synthesis step does not work as expected.[41]

Forms of LSD

LSD is produced in crystalline form and then mixed with excipients or diluted as a liquid for production in ingestible forms. Liquid solution is either distributed as-is in small vials or, more commonly, sprayed or soaked onto a distribution medium. Historically, LSD solutions were first sold on sugar cubes, but practical considerations forced a change to tablet form. Early pills or tabs were flattened on both ends and identified by color: "grey flat", "blue flat", and so forth. Next came "domes", which were rounded on one end, then "double domes" rounded on both ends, and finally small tablets known as "microdots". Later still, LSD began to be distributed in thin squares of gelatin ("window panes") and, most commonly, as blotter paper: sheets of paper impregnated with LSD and perforated into small squares of individual dosage units. The paper is then cut into small square pieces called "tabs" for distribution. Individual producers often print designs onto the paper serving to identify different makers, batches or strengths, and such "blotter art" often emphasizes psychedelic themes.

LSD is sold under a wide variety of street names including Acid, Trips, Alice Dee, 'Cid/Sid, Barrels, Blotter, Doses, "L", Liquid, Liquid A, Microdots, Mind detergent, Orange cubes, Orange micro, Owsley, Hits, Paper acid, Sacrament, Sandoz, Sugar, Sugar lumps, Sunshine, Tabs, Ticket, Twenty-five, Wedding bells, Windowpane, etc., as well as names that reflect the designs on the sheets of blotter paper.[42] On occasion, authorities have encountered the drug in other forms — including powder or crystal, and capsule. More than 200 types of LSD tablets have been encountered since 1969 and more than 350 paper designs have been observed since 1975. Designs range from simple five-point stars in black and white to exotic artwork in full four-color print.

Legal status

The United Nations Convention on Psychotropic Substances (adopted in 1971) requires its parties to prohibit LSD. Hence, it is illegal in all parties to the convention, which includes the United States, Australia and most of Europe. However, enforcement of extant laws varies from country to country.

LSD is easy to conceal and smuggle. A tiny vial can contain thousands of doses. Not much money is made from retail-level sales of LSD, so the drug is typically not associated with the violent organized criminal organizations involved in cocaine and opiate smuggling.

United States: Prior to 1967

Prior to 1967, LSD was available legally in the United States as an experimental psychiatric drug. (LSD "apostle" Al Hubbard actively promoted the drug between the 1950s and the 1970s and introduced thousands of people to it.) The US Federal Government classified it as a Schedule I drug according to the Controlled Substances Act of 1970. As such, the Drug Enforcement Administration holds that LSD meets the following three criteria: it is deemed to have a high potential for abuse; it has no legitimate medical use in treatment; and there is a lack of accepted safety for its use under medical supervision. (LSD prohibition does not make an exception for religious use.) Lysergic acid and lysergic acid amide, LSD

precursors, are both classified in Schedule III of the Controlled Substances Act. Ergotamine tartrate, a precursor to lysergic acid, is regulated under the Chemical Diversion and Trafficking Act.

LSD has been manufactured illegally since the 1960s. Historically, LSD was distributed not for profit, but because those who made and distributed it truly believed that the psychedelic experience could do good for humanity, that it expanded the mind and could bring understanding and love. A limited number of chemists, probably fewer than a dozen, are believed to have manufactured nearly all of the illicit LSD available in the United States. The best known of these is undoubtedly Augustus Owsley Stanley III, usually known simply as Owsley. The former chemistry student set up a private LSD lab in the mid-Sixties in San Francisco and supplied the LSD consumed at the famous Acid Test parties held by Ken Kesey and his Merry Pranksters, and other major events such as the Gathering of the tribes in San Francisco in January 1967. He also had close social connections to leading San Francisco bands the Grateful Dead, Jefferson Airplane and Big Brother and The Holding Company, regularly supplied them with his LSD and also worked as their live sound engineer and made many tapes of these groups in concert. Owsley's LSD activities — immortalized by Steely Dan in their song "Kid Charlemagne" — ended with his arrest at the end of 1967, but some other manufacturers probably operated continuously for 30 years or more. Announcing Owsley's first bust in 1966, The San Francisco Chronicle's headline "LSD Millionaire Arrested" inspired the rare Grateful Dead song "Alice D. Millionaire."

United States: 1970 to the present

American LSD usage declined in the 1970s and 1980s, then experienced a mild resurgence in popularity in the 1990s. Although there were many distribution channels during this decade, the U.S. DEA identified continued tours by the psychedelic rock band The Grateful Dead and the then-burgeoning rave scene as primary venues for LSD trafficking and consumption. American LSD usage fell sharply circa 2000. The decline is attributed to the arrest of two chemists, William Leonard Pickard, a Harvard-educated organic chemist, and Clyde Apperson. According to DEA reports, black market LSD availability dropped by 95% after the two were arrested in 2000. These arrests were a result of the largest LSD manufacturing raid in DEA history.[43]

Pickard was an alleged member of the Brotherhood of Eternal Love group that produced and sold LSD in California during the late 1960s and early 1970s. It is believed he had links to other "cooks" associated with this group — an original source of the drug back in the 1960's — and his arrest may have forced other operations to cease production, leading to the large decline in street availability.

The DEA claims these two individuals were responsible for the vast majority of LSD sold illegally in the United States and a significant amount of the LSD sold in Europe, and that they worked closely with organized traffickers. While this claim may have some bearing, the extent of Pickard's direct influence on the overall availability in the United States is not fully known. Some attest that "Pickard's Acid" was sold exclusively in Europe, and was not distributed through American music venues.

In November of 2003, Pickard was sentenced to life imprisonment without parole, and Apperson was sentenced to 30 years imprisonment without parole, after being convicted in Federal Court of running a large scale LSD manufacturing operation out of several clandestine laboratories, including a former missile silo near Wamego, Kansas.

LSD manufacturers and traffickers can be categorized into two groups: A few large scale producers, such as the aforementioned Pickard and Apperson, and an equally limited number of small, clandestine chemists, consisting of independent producers who, operating on a comparatively limited scale, can be found throughout the country. As a group, independent producers are of less concern to the Drug Enforcement Agency than the larger groups, as their product reaches only local markets.

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See also

Chemical

- Entheogen

- Psychedelic drug
- Psychedelics, dissociatives and deliriants
- Psychoactive drug
    - Related chemical compounds: ergolines, LSA, psilocybin, DMT, serotonin

Other

- Dimethyltryptamine - A LSD like drug created by the human body

Psychedelic tryptamines

Alphamethyltryptamine | Psilocin | Psilocybin

Alphamethyltryptamine

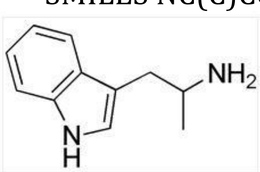
+- - Methyl-tryptamine

Chemical formula C***11***H***14***N***2***

Molecular mass 174.24 g/mol

CAS number 299-26-3

SMILES NC(C)CC1=CNC2=C1C=CC=C2



±-methyl-tryptamine, also known as *±-MT*, AMT or IT-290, is a synthetic drug of the tryptamine family. First developed as an antidepressant, in the 1960s it was produced commercially for this purpose in the Soviet Union under the trade name "Indopan" in 5mg and 10mg pills. Like many other tryptamines, at sufficient dosages it is a psychedelic hallucinogen. Its effects may take 2-3 hours to onset, and can last for 18 to 24 hours. It also acts as a monoamine oxidase inhibitor and a stimulant, the latter property possibly being related to similarities in chemical structure to amphetamine. On 4 April 2003, an emergency

United States DEA order resulted in ±-MT being placed, along with 5-MeO-DIPT, on Schedule I of the Controlled Substances Act.

Chemistry

±-Methyl-=tryptamine= is chemically related to serotonin, an important neurotransmitter. It acts by mimicking the effects of serotonin at the 5-HT2 receptor and by interfering with neurotransmitter reuptake and degradation mechanisms. ±-MT has a stereocenter, and S-(+)-±-MT is the more active stereoisomer.

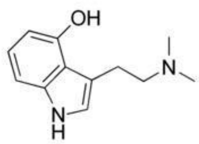
Dosage

An oral dosage of 5-10mg will produce a stimulating effect, and 20-30mg usually results in hallucinogenic effects that can last 24 hours. While a dosage of 60-80mg is generally considered a strong dosage, some users have been known to use large amounts of ±-MT, and report dosages of up to 150mg being taken. The freebase can also be smoked, and 5-20mg is generally used.

Effects

AMT is a long-acting psychedelic/euphoric stimulant. It is known to cause nausea and vomiting in many recreational users.

Psilocin



Systematic name 4-Hydroxy-N,N-dimethyl-tryptamine

Other names 3-(2-(Dimethylamino)ethyl)- 1H-indol-4-ol

Molecular formula C***12***H***16***N***2***O

SMILES *OC1=CC=CC2=C1C(CCN(C)C)=CN2*

Molar mass 204.27 g/mol

CAS number [520-53-6]

Properties

Melting point 173 - 176 °C (base)

Except where noted otherwise, data are given for materials in their standard state (at 25 °C, 100 kPa)

Psilocin, sometimes misspelled psilocine or psilotsin, is a psychedelic (hallucinogenic) mushroom alkaloid. It is found in most psychedelic mushrooms together with its close congener psilocybin. Psilocin is a Schedule I drug under the Convention on Psychotropic Substances.[1]

History

The Swiss chemist Albert Hofmann and the laboratory assistant Hans Tscherter from Sandoz isolated psilocin and its phosphate ester psilocybin from Psilocybe mushrooms in 1959 guided by self-administration.

Chemistry

Psilocin can be obtained by dephosphorylation of natural psilocybin under strongly acidic or under alkaline conditions (hydrolysis). One synthetic route uses the Speeter-Anthony tryptamine synthesis starting from 4-hydroxyindole.

Psilocin is relatively unstable in solution due to its phenolic OH group. Under alkaline conditions in the presence of oxygen it immediately forms bluish and dark black degradation products. Similar products are also formed under acidic conditions in the presence of oxygen and Fe^{3+} ions (Keller's reagent, $FeCl_3$ / MeOH / HCl). Psilocin is an amine and forms salts

with acids that are usually more stable upon storage. Psilocin base can be evaporated by heating.

Pharmacology

Psilocin is the pharmacologically active agent in the body after ingestion of psilocybin or psychedelic mushrooms.

See psilocybin for more details.

See also

- Psilocybin
- Psychedelic drug
- Psychoactive drug
- Ayahuasca
- Soma

References

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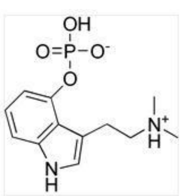
Psilocybin



Systematic name 4-Phosphoryloxy-N,N- dimethyl-tryptamine

Molecular formula $C_{12}H_{17}N_2O_4P$

SMILES C[N+](C)([H])CCC1=CNC2= C1C(OP([O-])(O)=O)=CC=C2

Molar mass 284.25 g/mol

CAS numbe [520-52-5]

Except where noted otherwise, data are given for materials in their standard state (at 25 °C, 100 kPa)

Psilocybin (also known as *psilocybine*), is a psychedelic alkaloid of the tryptamine family. It is present in many species of fungi, including those of the genus Psilocybe, such as Psilocybe cubensis and Psilocybe semilanceata, but also reportedly isolated from a dozen or so other genera. Psilocybin-containing mushrooms are commonly called magic mushrooms or simply "shrooms". Effects of psilocybin are comparable to LSD, but last for a shorter time, although intensity and duration vary depending on dosage, individual physiology, and set and setting.

Chemistry

Psilocybin is a prodrug that is converted into the pharmacologically active compound psilocin in the body by dephosphorylation. This chemical reaction takes place under strongly acidic conditions or enzymatically by phosphatases in the body. Psilocybin is a zwitterionic alkaloid that is soluble in water, moderately soluble in methanol and ethanol, and insoluble in most organic solvents.

Albert Hofmann was the first to recognize the importance and chemical structure of the pure compounds psilocybin and psilocin. Hoffmann was aided in this process by his willingness to ingest extracts isolated from Psilocybe. Hofmann's colleagues at the University of Delaware (who were receiving funding from a Central Intelligence Agency front company) were also trying to isolate the active principle, but were unsuccessful.[1]

Biology

Psilocybin is a naturally-occurring compound found in high concentrations in some species of Psilocybe and Panaeolus (collectively called "psilocybin mushrooms" or "psilocybian mushrooms"), and at low levels in a large number of species of the Agaricales. The spores of these mushrooms are completely free of both psilocybin and psilocin. The total potency varies greatly between species and even between specimens of one species in the same batch. Younger, smaller mushrooms are relatively higher in alkaloids and have a milder taste than larger, mature mushrooms. Mature mycelium contains some amount of psilocybin, which can be extracted with an acidic solution, usually of citric acid or ascorbic acid (Vitamin C). Young mycelium (recently germinated from spores) does not contain appreciable amounts of alkaloids. Most species of hallucinogenic mushrooms also contain small amounts of the psilocybin analogs baeocystin and norbaeocystin. Many types of psilocybin mushrooms bruise blue when handled or damaged — this is due to the oxidization of active compounds and is most notable in mushrooms with a high psilocin content. Several other non-psychoactive (and in some cases toxic) mushrooms also bruise blue.

Pharmacology

Psilocybin is rapidly dephosphorylated in the body to psilocin which then acts as a partial agonist at the 5-HT2A serotonin receptor in the brain where it mimics the effects of serotonin (5-HT).

Medicine

Psilocybin has been studied as a treatment for several disorders. In the early 1960s, Timothy Leary and Richard Alpert ran the Harvard Psilocybin Project, carrying out a number of experiments concerning the use of psilocybin in the treatment of personality disorders and other uses in psychological counseling.

More recently, in the US, an FDA-approved study supported by Multidisciplinary Association for Psychedelic Studies (MAPS) began in 2001 to study the effects of psilocybin on patients with obsessive-compulsive disorder. MAPS has also proposed studying psilocybin's potential application for the treatment of cluster headaches based on anecdotal evidence presented to them by a group of cluster headache sufferers.

Toxicity

The toxicity of psilocybin is relatively low; when administered intravenously in rabbits, Psilocybin's LD50 is approximately 12.5mg/kg. In rats, the LD50 is 280mg/kg -- almost one and a half times that of caffeine.[1] Death from psilocybin intake alone is unknown at most recreational or medicinal levels.

The psilocybin content of psychoactive mushrooms is quite variable and depends on species, growth and drying conditions, and mushroom size, but averages around 5mg/g of dried mushroom, or 1mg/2g of fresh mushroom.

Effects

Psilocybin is absorbed through the lining of the mouth and stomach. Effects begin 20-45 minutes after ingestion of psilocybin-containing mushrooms, and last from 2-6 hours depending on dose, species, and individual metabolism. Typical recreational dosage is from 10-50mg Psilocybin, or approximately 2-5g dried mushroom.

The effects of psilocybin are often pleasant, even ecstatic, including a deep sense of connection to others, confusion, hilarity, and a general feeling of connection to nature and the universe. Difficult trips may occur when psychedelic compounds are taken in a non-supportive or inadequate environment, by an inexperienced person, or in an unexpectedly high dose.

At low doses, hallucinatory effects occur, including walls that seem to breathe, a vivid enhancement of colors and the animation of organic shapes. At higher doses, experiences tend to be less social and more entheogenic, often catalyzing intense spiritual experiences. For example, in the Marsh Chapel Experiment, which was run by a graduate student at Harvard Divinity School under the supervision of Timothy Leary, almost all of the graduate degree divinity student volunteers who received psilocybin reported profound religious experiences. (A brief video about the Marsh Chapel experiment can be viewed here.)

In 2006, a group of researchers from Johns Hopkins School of Medicine led by Roland R Griffiths conducted an experiment assessing the degree of mystical experience and attitudinal effects of the psilocybin experience; this report was published in the journal Psychopharmacology. Thirty-six volunteers without prior experience with hallucinogens were given psilocybin and methylphenidate (Ritalin) in separate sessions, the methylphenidate sessions serving as a control and active placebo; the tests were double-blind, with neither the subject nor the administrator knowing which drug was being administered. The degree of mystical experience was measured using a questionnaire on mystical experience developed by Ralph W Hood; 61% of subjects reported a "complete mystical experience" after their psilocybin session, while only 13% reported such an outcome after their experience with methylphenidate. Two months after taking psilocybin, 79% of the participants reported moderately to greatly increased life satisfaction and sense of well-being. About 36% of participants also had a strong to extreme “experience of fear” or dysphoria (eg, a “bad trip”) at some point during the psilocybin session (which was not reported by any subject during the methylphenidate session), with about one-third of these (13% of the total) reporting that this dysphoria dominated the entire session. These negative effects were reported to be easily managed by the researchers and did not have a lasting negative effect on the subject’s sense of well-being. This research was widely covered in the major media outlets.

A very small number of people are unusually sensitive to psilocybin's effects, where doses as little as 0.25 grams of dried Psilocybe cubensis mushrooms (normally a threshold dose of around 2 mg psilocybin) can result in effects usually associated with medium and high doses. Likewise, there are some people who require relatively high doses of psilocybin to gain low-dose effects. Individual brain chemistry and metabolism plays a large role in determining a person's response to psilocybin.

Psilocybin is metabolized mostly in the liver where it becomes psilocin. It is broken down by the enzyme monoamine oxidase. MAO inhibitors have been known to sustain the effects of psilocybin for longer periods of time; people who are taking an MAOI for a medical condition (or are seeking to potentiate the mushroom experience) should be careful.

Mental and physical tolerance to psilocybin builds and dissipates quickly. Taking psilocybin more than three or four times in a week (especially two days in a row) can result in diminished effects. Tolerance dissipates after a few days, so frequent users often keep doses spaced five to seven days apart to avoid the effect.

Adverse effects

The consumption may cause Hallucinogen persisting perception disorder (HPPD).[2]

It is also possible that a user will take foolish risks, such as driving a vehicle, while under the influence of this or any other psychoactive compound.

Most other adverse effects come from contaminants.

Social and legal aspects

Psilocybin and psilocin are listed as Schedule I drugs under the United Nations 1971 Convention on Psychotropic Substances.[5] Schedule I drugs are illicit drugs that are claimed to have no known therapeutic benefit. Parties to the treaty are required to restrict use of the drug to medical and scientific research under strictly controlled conditions. Most national drug laws have been amended to reflect this convention (for example, the US Psychotropic Substances Act, the UK Misuse of Drugs Act 1971, and the Canadian Controlled Drugs and Substances Act), with possession and use of psilocybin and psilocin being prohibited under almost all circumstances, and often carrying severe legal penalties.

Possession and use of psilocybin mushrooms, including the bluing species of Psilocybe, is therefore prohibited by extension. However, in many national, state, and provincial drug laws, there is a great deal of ambiguity about the legal status of psilocybin mushrooms and the spores of these mushrooms, as well as a strong element of selective enforcement in some places. For more details on the legal status of psilocybin mushrooms and Psilocybe spores, see: Psilocybe: Social and legal aspects.

Because of the ease of cultivating psilocybin mushrooms or gathering wild species, purified psilocybin is practically nonexistent on the illegal drug market.

See also

- Psilocin
- Psychedelic drug
- Psychoactive drug
- Ayahuasca
- Soma

References

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2. ^ Espiard ML. et al. (2005): "HPPD after psilocybin consumption: a case study.", Eur. Psychiatry 20(5-6):458-60. Abstract

Kolokol-1

KOLOKOL-1 (russian >;>:>;, eng. bell) is an opiate-derived incapacitating agent. Although the exact nature of the active chemical has not been revealed, in all likelihood it is a derivative of the drug fentanyl, possibly the extraordinarily potent carfentanil. It takes effect very quickly, within one to three seconds, reportedly rendering its victims unconscious for two to six hours. Little else is known about this agent.

According to Lev Fyodorov, a former Soviet chemical weapons scientist who now heads the independent Council for Chemical Security in Moscow, the gaseous agent was originally developed around a secret military research facility in Leningrad during the 1970s. Methods of dispersing it were later developed and tested by releasing harmless bacteria through subway system ventilation shafts first in Moscow and then in Novosibirsk. Fyodorov also claimed that leaders of the failed August 20, 1991 Communist coup considered using the agent in the Russian parliament building. [1]

Use in the Moscow theatre siege

In 2002, Chechen terrorists took a large number of hostages in the Moscow theatre siege, and threatened to blow up the entire theatre if any attempt was made to break the siege. By the third day of the crisis, the Chechens demanded that Russian president Vladimir Putin begin withdrawing Russian troops from Chechnya, or they would begin killing hostages.

Writing in the Moscow daily Komsomolskaya Pravda, Viktor Baranets, a former Russian Defense Ministry official, stated that the Ministry of the Interior knew that any normal riot control agent, such as pepper spray or tear gas, would allow the terrorists time to harm the hostages. They decided to use the strongest agent available. The paper identified the material as a KGB-developed "psycho-chemical gas" known as "Kolokol-1", and reported that "the gas had such an influence on [Chechen siege leader Movsar] Barayev that he couldn't get up from [his] desk". [2]

Immediately after the siege, Western media speculated widely as to the identity of the substance that was used to end the siege, and chemicals such as the tranquilizer diazepam (Valium), the anticholinergic BZ, the oripavine etorphine, and the anaesthetic halothane were proposed. Two days after the incident the Russian Health Minister Yuriy Shevchenko told a news conference that the gas was "based on a derivative of fentanyl". [3]

Although the exact nature of the active chemical has not been verified, the Russian language newspaper Gazeta claimed that the chemical used had been trimethylfentanyl, which is an opioid, attributing this information to "experts from the Moscow State University chemistry department". The name may be a mistranslation of "3-methyl fentanyl", a superpotent fentanyl analog that is about 1000-times more potent than morphine, that was manufactured and abused in the former USSR.

Questionable non-lethality

If Kolokol-1 was the incapacitating agent used in the Moscow theatre siege, it appears that it was directly or indirectly responsible for the deaths of over 100 of the 700 hostages, who appear to have died through a combination of the effects of high doses of the incapacitating substance, lack of food and water, and the lack of adequate medical treatment following the raid, which was exacerbated by the refusal of the authorities to reveal to doctors the nature of the incapacitating agent.

References

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2. ^ Peterson, Scott. (October 29, 2002). "Gas enters counterterror arsenal". The Christian Science Monitor, WORLD; p. 1.
3. ^ (2002) "News Chronology (August through October 2002)". THE CBW CONVENTIONS BULLETIN (Issue 58), 27-46.

Psychedelia

Psychedelia is a term describing a category of music, visual art, fashion, and culture that is associated originally with the high 1960s, hippies, and the Haight-Ashbury neighborhood of San Francisco, California. It generally began in 1966, but truly took off in 1967 with the Summer of Love. Its beginnings are associated with San Francisco but the style soon spread across the U.S.A., and worldwide.

Psychedelia takes its name from psychedelic (mind manifesting) drugs, which assisted in fueling an entire subculture of fusing together different genres and mediums where strong boundaries had previously existed.

The counterculture of the 1960s had a strong influence on the popular culture of the early 1970s, and is well recognized even by those who are naïve to its psychedelic origins. and is also known as the best art of writing ever known

See also

- Psychedelic

Hallucination

A *hallucination* is a sensory perception experienced in the absence of an external stimulus, as distinct from an illusion, which is a misperception of an external stimulus. Hallucinations may occur in any sensory modality - visual, auditory, olfactory, gustatory, tactile, or proprioception (sense of balance and position in space).

Prevalence and types of hallucinatory experience

Studies have shown hallucinatory experiences take place across the population as a whole. Previous studies, one as early as 1894[1], have reported that approximately 10% of the population experience hallucinations. A recent survey of over 13,000 people[2] reported a much higher figure with almost 39% of people reported hallucinatory experiences, 27% of which reported daytime hallucinations, mostly outside the context of illness or drug use. From this survey, olfactory (smell) and gustatory (taste) hallucinations seem the most common in the general population.

Hypnagogic hallucinations and hypnopompic hallucinations are considered normal phenomena. Hypnagogic hallucinations can occur as one is falling asleep and hypnopompic hallucinations occur when one is waking up.

Auditory hallucinations (particularly of one or more talking voices) are particularly associated with psychotic disorders such as schizophrenia, and hold special significance in diagnosing these conditions despite the fact that 'hearing voices' is not a sign of mental illness.

Florid hallucinations are usually associated with drug use (particularly hallucinogenic drugs), sleep deprivation, psychosis or neurological illness.

Scientific explanations

Various theories have been put forward to explain the occurrence of hallucinations. When psychodynamic (Freudian) theories were popular in psychiatry, hallucinations were seen as a projection of unconscious wishes and desires. As biological theories have become orthodox, hallucinations are more often thought of (by psychiatrists at least) as being caused by functional deficits in the brain. With reference to mental illness, the function (or dysfunction) of the neurotransmitter dopamine is thought to be particularly important[3].

Psychological research has argued that hallucinations may result from biases in what are known as metacognitive abilities[4]. These are abilities that allow us to monitor or draw inferences from our own internal psychological states (such as intentions, memories, beliefs and thoughts). The ability to discriminate between self-generated and external sources of information is considered to be an important metacognitive skill and one which may break down to cause hallucinatory experiences.

Visual Hallucination Subtypes

Hypnagogic Hallucination

These hallucinations occur just before falling asleep and affect a surprising number of people in the population. The hallucinations can last from seconds to minutes, all the while the subject usually remains aware of the true nature of the images. These are usually associated with narcolepsy, but can also affect non-narcoleptics. Hypnagogic hallucinations are sometimes associated with brainstem abnormalities, but this is rare. [5].

Peduncular Hallucinosis

Peduncular means pertaining to the peduncle, which is a name given to a neural tract running to and from the pons. These hallucinations occur most often in the evenings, but not during drowsiness as in the case above. The subject is usually fully conscious and can interact with the hallucinatory characters for extended periods of time. As in the case of hypnagogic hallucinations, insight into the nature of the images remains intact. The false images can occur in any part of the visual field, and are rarely polymodal. [6].

Delirium Tremens

One of the most enigmatic forms of visual hallucinations are the highly variable, possibly polymodal Delirium Tremens. As the name suggests, the subject is usually agitated and confused, especially in the later stages of this disease. Insight is gradually reduced with the progression of this disorder. Sleep is disturbed and short, with REM overflow. [7].

Parkinson's disease and Lewy body Dementia

Parkinson's disease is linked with Lewy body Dementia for their similar hallucinatory symptoms. The symptoms strike during the evening in any part of the visual field and are rarely polymodal. The segue into hallucinations may start with illusions [8] where sensory perception is greatly distorted, but no novel sensory information is present. These typically last for several minutes, during which time the subject may be either conscious and normal or drowsy/inaccessable. Insight into these hallucinations is usually preserved and REM sleep is usually reduced. Parkinson's disease is usually associated with a degraded substantia nigra pars compacta, but recent evidence suggests that PD affects a handful of other sites in the brain. Some places of noted degradation include the median raphe nuclei, the noradrenergic parts of the locus coeruleus and the cholinergic neurons in the parabrachial and pedunculopontine nuclei of the tegmentum. [9].

Migraine Coma

This type of hallucination is usually experienced during the recovery from a comatose state. The migraine coma can last for up to two days and a state of depression is sometimes comorbid. The hallucinations occur during states of full consciousness and insight into the hallucinatory nature of the images is preserved. It has been noted that ataxic lesions accompany the migraine coma.[10].

Charles Bonnet Syndrome

Charles Bonnet Syndrome is the name given to visual hallucinations experienced by blind patients. The hallucinations can usually be dispersed by opening or closing the eyelids until the visual images disappear. The hallucinations usually occur during the morning or evening, but are not dependent on low light conditions. These prolonged hallucinations usually do not disturb the patients very much as they are aware that they are hallucinating. [11].

Focal Epilepsy

The visual hallucinations from focal epilepsy are characterized by being brief, and stereotyped. They are usually localized to one part of the visual field and last only a few seconds. Other epileptic features may present themselves between visual episodes. Consciousness is usually impaired in some way, but nevertheless insight into the

hallucination is preserved. Usually this type of focal epilepsy is caused by a lesion in the posterior temporoparietal. [12].

Paranormal theories

A rarely expressed but persistent alternate explanation of hallucinations, espoused by non-materialists, is that people prone to hallucinations can sometimes perceive non-physical phenomena such as angels, visions or the voices of departed spirits or demons. For this reason, a hallucination may also be classified as an anomalous phenomenon, when no suitable scientific explanation is verified.

See also

- Hallucinogenic drug
- LSD

Further reading

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Nutmeg

Scientific classification

Kingdom: Plantae
Division: Magnoliophyta
Class: Magnoliopsida
Order: Magnoliales
Family: Myristicaceae
Genus: *Myristica* Gronov.

Species

About 100 species, including:

- Myristica argentea
- Myristica fragrans
- Myristica malabarica

The *nutmegs Myristica* are a genus of evergreen trees indigenous to tropical southeast Asia and Australasia. They are important for two spices derived from the fruit, *nutmeg* and *mace*.

Nutmeg is the actual seed of the tree, roughly egg-shaped and about 20-30 mm long and 15-18 mm wide, and weighing between 5 and 10 grams dried, while mace is the dried "lacy" reddish covering or arillus of the seed.

Several other commercial products are also produced from the trees, including essential oils, extracted oleoresins, and nutmeg butter (see below).

The pericarp (fruit/pod) is used in Grenada to make a jam called Morne Delice. In Indonesia, the fruit is sliced finely, cooked and crystallised to make a fragrant candy called manisan pala ("nutmeg sweets").

The most important species commercially is the Common or Fragrant Nutmeg Myristica fragrans, native to the Banda Islands of Indonesia; it is also grown in the Caribbean, especially in Grenada. Other species include Papuan Nutmeg M. argentea from New Guinea, and Bombay Nutmeg M. malabarica from India; both are used as adulterants of M. fragrans products.

Culinary uses

Nutmeg and mace have similar taste qualities, nutmeg having a slightly sweeter and mace a more delicate flavor. Mace is often preferred in light-coloured dishes for the bright orange, saffron-like colour it imparts. It is nice in cheese sauces and is best grated fresh.

In Indian cuisine, nutmeg is used almost exclusively in sweets. It is known as jaiphal in most parts of India. It is also used in small quantities in garam masala.

In other European cuisine, nutmeg and mace are used especially in potato dishes and in processed meat products; they are also used in soups, sauces and baked goods.

Japanese varieties of curry powder include nutmeg as an ingredient.

Nutmeg is a traditional ingredient in mulled cider, mulled wine, and eggnog.

Essential oils

The essential oil is obtained by the steam distillation of ground nutmeg and is used heavily in the perfumery and pharmaceutical industries. The oil is colorless or light yellow and smells and tastes of nutmeg. It contains numerous components of interest to the oleochemical industry, and is used as a natural food flavouring in baked goods, syrups (e.g. Coca Cola), beverages, sweets etc. It replaces ground nutmeg as it leaves no particles in the food. The essential oil is also used in the cosmetic and pharmaceutical industries for instance in tooth paste and as major ingredient in some cough syrups. In traditional medicine nutmeg and nutmeg oil were used for illnesses related to the nervous and digestive systems. Myristicin and elemicin are believed to be the chemical constituents responsible for the subtle hallucinogenic properties of nutmeg oil. Other known chemical ingredients of the oil are ±-pinene, sabinene, ^{3}-terpinene and safrole.

Externally, the oil is used for rheumatic pain and, like clove oil, can be applied as an emergency treatment to dull toothache. Put 1-2 drops on a cotton swab, and apply to the gums around an aching tooth until dental treatment can be obtained. In France, it is given in drop doses in honey for digestive upsets and used for bad breath. Use 3-5 drops on a sugar lump or in a teaspoon of honey for nausea, gastroenteritis, chronic diarrhea, and indigestion.

Alternatively a massage oil can be created by diluting 10 drops in 10 ml almond oil. This can be used for muscular pains associated with rheumatism or overexertion. It can also be combined with thyme or rosemary essential oils. To prepare for childbirth, massaging the

abdomen daily in the three weeks before the baby is due with a mixture of 5 drops nutmeg oil and no more than 5 drops sage oil in 25 ml almond oil has been suggested.

Nutmeg butter

Nutmeg butter is obtained from the nut by expression. It is semi solid and reddish brown in colour and tastes and smells of nutmeg. Approximately 75% (by weight) of nutmeg butter is trimyristin which can be turned into myristic acid, a 14-carbon fatty acid which can be used as replacement for cocoa butter, can be mixed with other fats like cottonseed oil or palm oil, and has applications as an industrial lubricant.

History

There is some evidence that Roman priests may have burned nutmeg as a form of incense, although this is disputed. It is known to have been used as a prized and costly spice in the Middle Ages. Saint Theodore the Studite was famous for allowing his monks to sprinkle nutmeg on their pease pudding when required to eat it. In Elizabethan times it was believed that nutmeg could ward off the plague, so nutmeg was very popular. Nutmeg was traded by Arabs during the Middle Ages in the profitable Indian Ocean trade.

In the late 15th century, Portugal theoretically took over the Indian Ocean trade, including nutmeg, under the Treaty of Tordesillas with Spain and a separate treaty with the sultan of Ternate. But their control of this trade was always only partial and they remained largely participants, rather than overlords. The authority Ternate held over the nutmeg-growing centre of the Banda Islands was quite limited, and the Portuguese failed to gain a serious foothold in the islands themselves. The trade in nutmeg later became dominated by the Dutch in the 17th century, who managed to establish control over the Banda Islands after an extended military campaign that culminated in the massacre or expulsion of most of the islands' inhabitants in 1621. Thereafter, the Banda Islands were run as a series of plantation estates, with the Dutch mounting annual expeditions in local war-vessels to extirpate nutmeg trees planted elsewhere.

As a result of the British interregnum during the Napoleonic Wars, the English took temporary control of the Banda Islands from the Dutch and transplanted nutmeg trees to their own colonial holdings elsewhere, notably Zanzibar and Grenada.

Connecticut gets its nickname ("the Nutmeg State", "Nutmegger") from the legend that some unscrupulous Connecticut traders would whittle "nutmeg" out of wood, creating a "wooden nutmeg" (a term which came to mean any fraud).

World production

World production of nutmeg is estimated to average between 10,000 and 12,000 tonnes per year with annual world demand estimated at 9,000 tonnes; production of mace is estimated at 1,500 to 2,000 tonnes. Indonesia and Grenada dominate production and exports of both products with a world market share of 75% and 20% respectively. Other producers include India, Malaysia, Papua New Guinea, Sri Lanka and Caribbean islands such as St.

Vincent. The principal import markets are the European Community, the United States, Japan and India. Singapore and the Netherlands are major re-exporters.

A possible future use for nutmeg is as a natural control for insects that infest stored cereal grains.

At one time, nutmeg was one of the most valuable spices. It has been said that in England, several hundred years ago, a few nutmeg nuts could be sold for enough money to enable financial independence for life.

The first harvest of nutmeg trees takes place 7-9 years after planting and the trees reach their full potential after 20 years.

Risks and toxicity

In low doses, nutmeg produces no noticeable physiological or neurological response. Large doses of 7.5 g or more are dangerous, potentially inducing convulsions, palpitations, nausea, eventual dehydration, and generalized body pain. In amounts of 1.0 g or more it is a mild to medium hallucinogen, producing visual distortions and a mild euphoria. Nutmeg contains chemicals called MAO inhibitors (MAOIs), which disable the brain's ability to stop amines, found in most common foods, from affecting the brain and body. A test was carried out on the substance which showed that, when ingested in large amounts, nutmeg takes on a similar chemical make-up to MDMA (ecstasy). However, use of nutmeg as a recreational drug is unpopular, because of its strong taste and sand-like texture. Also there are potential painful physical side effects, the risk of Nutmeg Psychosis (see below) and the inconveniently long span for which the effects of a single dose can persist. A user will not experience a peak until approximately six hours after ingestion, and effects can linger for up to three days afterwards. Any unpleasant side-effects would persist throughout this period.

A risk in any large-quantity ingestion of nutmeg is the sudden onset of *Nutmeg Psychosis*, an acute psychiatric disorder marked by hallucinations, excitement, thought disorder, a sense of impending death and agitation. Some cases have resulted in hospitalization and reportedly few who have experienced the effects of nutmeg poisoning recommend it or repeat the experience.

Even in smaller doses, nutmeg can still be toxic. Ingestion of as little as 3 g may cause dry mouth, fast pulse, fever, flushing and posibly death. It has Amphetamine-like effects and may cause the desire to ingest of large volumes of water. There is no specific antidote; the adverse effects wear off after 24 hours (or more) of rest.

Nutmeg is extremely toxic when injected intravenously. Nutmeg can also cause liver damage if used regularly in large quantities. Nutmeg has in the past been used as an abortifacient. Nutmeg may also be fatal if used regularly in large quantities, but this is not a problem while cooking, since small amounts are used.

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Sedatives

A *sedative* is a substance which depresses the central nervous system (CNS), resulting in calmness, relaxation, reduction of anxiety, sleepiness, slowed breathing, slurred speech, staggering gait, poor judgment, and slow, uncertain reflexes. Sedatives may be referred to as *tranquilizers*, depressants, anxiolytics, soporifics, sleeping pills, downers, or sedative-hypnotics. At high doses or when they are abused, many of these drugs can cause unconsciousness (see hypnotic) and death.

Types of sedatives

- Antidepressants
    - mirtazapine (Remeron®)
    trazodone (Desyrel®)
- Barbiturates
    - secobarbital (Seconal®)
    pentobarbital (Nembutal®)
    amobarbital (Amytal®)
- Benzodiazepines ("minor tranquilizers")
    - alprazolam **(Xanax®)**
    - diazepam (Valium®)
    - lorazepam (Atavan®)
    - Typical antipsychotics ("major tranquilizers")
        - fluphenazine (Prolixin®)
        - haloperidol (Haldol®)
        loxapine succinate (Loxitane®)
        perphenazine (Etrafon®, Trilafon®)
        prochlorperazine (Compazine®)
        thiothixene (Navane®)
        trifluoperazine (Stelazine®, Trifluoperaz®)
    - Atypical antipsychotics
        - clozapine (Clozaril®)
        quetiapine (Seroquel®)
        risperidone (Risperdal®)

ziprasidone (Geodon®) (It may make some people tired, while causing insomnia in others)

- olanzapine (Zyprexa®)

- Herbal sedatives
  - catnip

Valerian (plant)
Mandrake
Kava Kava

- Uncategorized sedatives
  - chloral hydrate (Noctec®)

- diethyl ether **(Ether)**

  - eszopiclone (Lunesta®)

ethchlorvynol (Placidyl®)
ethyl alcohol (alcoholic beverage)
gamma-hydroxybutyrate (GHB)
glutethimide (Doriden®)
meprobamate (Miltown®)
methaqualone (Sopor®, Quaalude®)
methyl trichloride (Chloroform)
methyprylon (Noludar®)
ramelteon (Rozerem®)
zaleplon (Sonata®)
zolpidem (Ambien®)
zopiclone (Imovane®, Zimovane®)

Therapeutic use

Doctors and nurses often administer sedation to patients in order to dull the patient's anxiety related to painful or anxiety-provoking procedures. Although sedatives do not relieve pain in themselves, they can be a useful adjunct to analgesics in preparing patients for surgery, and are commonly given to patients before they are anaesthetized, or before other highly uncomfortable and invasive procedures like cardiac catheterization or MRI. They increase tractability and compliance of children or troublesome or demanding patients.

Patients in intensive care units are almost always sedated (unless they are unconscious from their condition anyway).

Sedative dependence

All sedatives can cause physiological and psychological dependence when taken regularly over a period of time, even at therapeutic doses. When dependent users decrease or end use suddenly, they will exhibit withdrawal symptoms ranging from restlessness, insomnia and anxiety to convulsions and death. When users become psychologically dependent, they feel as if they need the drug to function although there is no biological dependence. In both types of dependence, finding and using the drug becomes the focus in life. Both physical and psychological dependence can be treated (see Sedative Dependence).

Abuse and overdoses

All sedatives can be abused, but barbiturates are responsible for most of the problems with sedative abuse due to their widespread "recreational" or non-medical use. People who have difficulty dealing with stress, anxiety or sleeplessness may overuse or become dependent on sedatives. Heroin users take them either to supplement their drug or to substitute for it. Stimulant users frequently take sedatives to calm excessive jitteriness. Others take sedatives recreationally to relax and forget their worries. Barbiturate overdose is a factor in nearly one-third of all reported drug-related deaths. These include suicides and accidental drug poisonings. Accidental deaths sometimes occur when a drowsy, confused user repeats doses. In the US, in 1998, a total of 70,982 sedative exposures were reported to US poison control centers, of which 2310 (3.2%) resulted in major toxicity and 89 (0.1%) resulted in death. About half of all the people admitted to emergency rooms in the US as a result of nonmedical use of sedatives have a legitimate prescription for the drug, but have taken an excessive dose or combined it with alcohol or other drugs. Others get sedatives from friends who have authentic prescriptions or by using fake prescriptions.

See also Other non-therapeutical use.

Sedatives and alcohol

Sedatives and alcohol are sometimes combined recreationally or carelessly. Since alcohol also is a strong CNS depressant that slows brain function and depresses respiration, the two substances contradict each other and this combination can prove fatal. Karen Ann Quinlan collapsed into a coma after swallowing alcohol and tranquilizers at a party in 1975. Her case

spurred worldwide discussion of the ethics surrounding termination of life-sustaining treatment.

Lookalikes

Lookalikes, or pills made to mimic the appearance and the effects of authentic sedatives, are sold on the street. Lookalikes may contain over-the-counter drugs, such as antihistamines, that cause drowsiness. Like any other drug that is illicitly manufactured and sold, their composition and effects cannot be predicted.

Sedatives and amnesia

Sedation can sometimes leave the patient with long-term or short-term amnesia. Lorazepam is one such pharmacological agent that can cause anterograde amnesia. Intensive Care Unit patients who receive higher doses over longer periods of time, typically via IV drip, are more likely to experience such side effects.

Sedative drugs and crime

The sedative GHB is known for its use as a date rape drug, administered to unsuspecting patrons in bars or guests at parties to reduce the intended victims' defenses.

See also

- Psychoactive drug

Imidazopyridine

The *imidazopyridines* are a class of nonbenzodiazepine drugs related (in terms of their effect) to benzodiazepines. They include:

- Zolpidem (Ambien)
Alpidem

Stimulants

Stimulants are drugs that increase the activity of the sympathetic nervous system and produce a sense of euphoria or the feeling of being more awake. Stimulants can be used as recreational drugs or therapeutic drugs to increase alertness. They are also used and sometimes abused to boost endurance and productivity as well as to suppress appetite. Examples of common stimulants include caffeine, Amphetamine, cocaine, Ritalin and ecstasy.

Stimulants is a name given to several groups of drugs that tend to increase alertness and physical activity. The groups include pharmaceuticals such as amphetamines and the street drugs commonly called "uppers" or "speed," and cocaine. The more widely abused stimulants are amphetamines and cocaine. Cocaine has limited commercial use and its sale and possession are strictly controlled. Amphetamines are sometimes prescribed by physicians, and their availability makes them prime candidates for misuse.

Used properly, amphetamines increase alertness and physical ability. They are often prescribed to counter the effects of narcolepsy, a rare disorder marked by episodes of uncontrollable sleep, and to help children with minimal brain dysfunction.

Amphetamines increase the heart and respiration rates, increase blood pressure, dilate the pupils of the eyes, and decrease appetite. Other side effects include anxiety, blurred vision, sleeplessness, and dizziness. Abuse of amphetamines can cause irregular heartbeat and even physical collapse. A common form of abuse of amphetamines is by people who use them to counter the effects of sleeping pills (barbiturates) taken the night before. This roller coaster effect is damaging to the body.

While amphetamine users may feel a temporary boost in self-confidence and power, the abuse of the drug can lead to delusions, hallucinations, and a feeling of paranoia. These feelings can cause a person to act in bizarre fashion, even violently. In most people, these effects disappear when they stop using the drug.

Amphetamines are stolen or acquired through scams involving pharmacists or physicians who are duped into writing prescriptions for the drugs. These illegally acquired drugs are either sold as is or reduced to yellowish crystals that can be ingested in a number of ways, including sniffing and by injection.

Another means of illegal sale of amphetamines involves "look-alike" drugs produced in illicit laboratories. One danger in these look-alikes is that the potency may vary from batch to batch. A person accustomed to using a weak look-alike may unwittingly suffer an overdose taking the same volume of a stronger look-alike.

Symptoms Amphetamines are psychologically addictive. Users become dependent on the drug to avoid the "down" feeling they often experience when the drug's effect wears off. This dependence can lead a user to turn to stronger stimulants such as cocaine, or to larger doses of amphetamines to maintain a "high". People who abruptly stop using amphetamines often experience the physical signs of addiction, such as fatigue, long periods of sleep, irritability, and depression. How severe and prolonged these withdrawal symptoms are depends on the degree of abuse.

That boost we get from that morning cup of coffee is the result of the caffeine that naturally occurs in coffee. Caffeine is a common stimulant and is found not only in coffee and tea, but also in soft drinks and other foods. It can also be bought over-the-counter in tablet form. Too much caffeine can cause anxiousness, headaches, and the "jitters." Caffeine is also addictive and a person who abruptly stops drinking coffee may experience withdrawal symptoms.

Cocaine

Main article: Cocaine

Cocaine is made from the leaves of the coca shrub, which grows in the mountain regions of South American countries such as Bolivia, Colombia, and Peru. In Europe and North America, the most common form of cocaine is a white crystalline powder. Most users insufflate it intranasally.

Crack cocaine is a smokeable form of cocaine. It is usually smoked in a pipe, glass tube, or foil. Cocaine and crack are powerful, but short-acting stimulant drugs. Crack in particular has strong but short-lived effects. Both drugs tend to make users feel more alert and energetic. Many users say that they feel very confident and physically strong. Common effects include dry mouth, sweating, loss of appetite, and increased heart and pulse rates. Excessive doses can cause death from respiratory failure or heart failure.

Caffeine

Main article: Caffeine

Caffeine is a drug that is found in tea, chocolate, coffee, many soft drinks particularly energy drinks, and cocoa. There is no law prohibiting the sale of any of these products in most countries. Caffeine stimulates the body, increasing heart rate and blood pressure, and alertness, making some people feel better and able to concentrate. Caffeine is a diuretic. Some people have suggested that children that consume a lot of caffeine may become hyperactive even after the caffeine has been metabolized.

MDMA

Main article: Methylenedioxymethamphetamine

Methylenedioxymethamphetamine (MDMA) is an illegally-manufactured drug that comes either in tablet or capsule form (known as ecstasy), as a powder or crystal. Stimulant effects of MDMA include increased blood pressure and heart rate, loss of appetite, rapid sweating, and a dry mouth and throat. It is unusual for an ecstasy pill to contain only MDMA; they often contain amounts of other drugs which may include any of a wide range of substances such as MDA, MDEA, MDBD, PCP, DXM, PMA, Ketamine, Caffeine, Amphetamine, Methamphetamine, Ephedrine, Pseudoephedrine, Aspirin, Paracetamol, Fentanyl and, in a small number of cases, Heroin, Cocaine, Mescaline, DOB, or LSD . In some cases the substance sold as ecstasy may not contain MDMA at all.it is measured in mm/hg.

Nicotine

Nicotine is an alkaloid found in the nightshade family of plants (Solanaceae), predominantly in tobacco, and in lower quantities in tomato, potato, eggplant (aubergine), and green pepper. Nicotine alkaloids are also found in the leaves of the coca plant. Nicotine

constitutes 0.3 to 5% of the tobacco plant by dry weight, with biosynthesis taking place in the roots, and accumulates in the leaves. It is a potent nerve poison and is included in many insecticides.

In lower concentrations, the substance is a stimulant and is one of the main factors responsible for the dependence-forming properties of tobacco smoking. Although pure nicotine is noncarcinogenic, its presence may inhibit the body's ability to cull aberrant cells.

Antidepressants

Main article: Antidepressant

Antidepressants are not considered stimulants, as they do not act directly on the sympathetic nervous system and generally do not produce an immediate effect on mood. A possible exception is bupropion (Wellbutrin), whose chemical and pharmacological properties are similar to those of amphetamines.

Other

Recently, there have been improvements in the area of stimulant pharmacology, producing a class of chemicals known as eugeroics, or good arousal. These stimulants tend to increase alertness without the peripheral (body) effects or addiction/tolerance/abuse potential of the traditional stimulants. They have minimal effect on sleep structure, and do not cause rebound hypersomnolence or "come down" effects. Currently, there are two stimulants in this class being used: modafinil and adrafinil, marketed as Provigil and Olmifon, respectively.

In Russia, Carphedon is sold as a general stimulant under the brand name Phenotropil.

See also

- Psychoactives
- Narcotics

Caffeine

Systematic name 1,3,7-trimethyl-1H-purine-2,6(3H,7H)-dione

Other names 1,3,7-trimethylxanthine, trimethylxanthine, theine, mateine, guaranine, methyltheobromine

Molecular formula C8H10N4O2

SMILES O=C1C2=C(N=CN2C)N(C(=O)N1C)C

Molar mass 194.19 g mol**1**

Appearance Odorless, white needles or powder

CAS number [58-08-2]

Properties

Density and phase 1.2 g/cm^3, solid

Solubility in water Slightly soluble

Other solvents Soluble in ethyl acetate, chloroform, pyrimidine, pyrrole, tetrahydrofuran solution; moderately soluble in alcohol, acetone; slightly soluble in petroleum ether, ether, benzene.

Melting point 237 °C

Boiling point 178 °C (sublimes)

Acidity (pK_a) 10.4 (40 °C)

Hazards

MSDS External MSDS

Main hazards May be fatal if inhaled, swallowed or absorbed through the skin.
Flash point N/A

RTECS number EV6475000

Except where noted otherwise, data are given for materials in their standard state (at 25 °C, 100 kPa)

Caffeine is a xanthine alkaloid compound that acts as a stimulant in humans. Caffeine is sometimes called *guaranine* when found in guarana, *mateine* when found in mate, and *theine* when found in tea. It is found in the leaves and beans of the coffee plant, in tea, yerba mate, and guarana berries, and in small quantities in cocoa, the kola nut and the Yaupon Holly. Overall, caffeine is found in the beans, leaves, and fruit of over 60 plants, where it acts as a natural pesticide that paralyzes and kills certain insects feeding upon them.

Caffeine is a central nervous system (CNS) stimulant, having the effect of temporarily warding off drowsiness and restoring alertness. Beverages containing caffeine, such as coffee, tea, soft drinks and energy drinks enjoy great popularity: caffeine is the world's most widely consumed psychoactive substance. In North America, 90% of adults consume caffeine daily.[1]

Many natural sources of caffeine also contain widely varying mixtures of other xanthine alkaloids, including the cardiac stimulants theophylline and theobromine and other substances such as tannins.

Sources

Caffeine content of select common food and drugs[2][3]		
Product	***Serving size***	***Caffeine per serving (mg)***
Caffeine tablet (Vivarin)	1 tablet	200
Excedrin tablet	1 tablet	65
Coffee, brewed	240 mL (8 US fl oz)	135*
Coffee, decaffeinated	240 mL (8 US fl oz)	5*
Coffee, espresso	57 mL (2 US fl oz)	100*
Chocolate, Dark (Hershey's Special Dark)	1 bar (43 g; 1.5 oz)	31
Chocolate, Milk (Hershey Bar)	1 bar (43 g; 1.5 oz)	10
Red Bull	240 mL (8.2 US fl oz)	80
Bawls Guarana	296 mL (10 US fl oz)	67
Soft drink, Mountain Dew "Dew Fuel"	355 mL (12 US fl oz)	54.5
Soft drink, Coca-Cola Classic	355 mL (12 US fl oz)	34
Atomic Rush	255 mL (7 US fl oz)	100
Tea, green	240 mL (8 US fl oz)	15
Tea, leaf or bag	240 mL (8 US fl oz)	50
* Estimated average caffeine content per serving. Actual content varies according to preparation.		

Caffeine is a plant alkaloid, found in numerous plant species, where it acts as a natural pesticide that paralyzes and kills certain insects feeding upon them.[4] The most commonly used caffeine-containing plants are coffee, tea, and to some extent cocoa. Other, less commonly used, sources of caffeine include the yerba mate[5] and guaraná plants, which are sometimes used in the preparation of teas and energy drinks. Two of caffeine's alternative names, mateine[6] and guaranine,[7] are derived from the names of these plants.

The world's primary source of caffeine is the coffee bean (the seed of the coffee plant), from which coffee is brewed. Caffeine content in coffee varies widely depending on the type of coffee bean and the method of preparation used;[8] even beans within a given bush can

show variations in concentration. In general one serving of coffee ranges from about 40 milligrams for a single shot (30 milliliters) of arabica-variety espresso to about 100 milligrams for strong drip coffee. Generally, dark-roast coffee has less caffeine than lighter roasts because the roasting process reduces the bean's caffeine content. Arabica coffee normally contains less caffeine than the robusta variety.[8] Coffee also contains trace amounts of theophylline, but no theobromine.

Tea is another common source of caffeine. Tea usually contains about half as much caffeine per serving as coffee, depending on the strength of the brew. Certain types of tea, such as black and oolong, contain somewhat more caffeine than most other teas. Tea contains small amounts of theobromine and slightly higher levels of theophylline than coffee. Preparation has a significant impact on tea, and color is a very poor indicator of caffeine content.[9] Teas like the green Japanese gyokuro, for example, contain far more caffeine than much darker teas like lapsang souchong, which has very little.

Chocolate derived from cocoa contains a small amount of caffeine. Chocolate is a weak stimulant, which is mostly due to its content of theobromine and theophylline.[10] It contains too little of these compounds for a reasonable serving to create effects in humans that are on par with coffee. A typical 28-gram serving of a milk chocolate bar has about as much caffeine as a cup of decaffeinated coffee.

Caffeine is also a common ingredient of soft drinks such as cola, originally prepared from kola nuts. Soft drinks typically contain about 10 to 50 milligrams of caffeine per serving. By contrast, energy drinks such as Red Bull contain as much as 80 milligrams of caffeine per serving. The caffeine in these drinks either originates from the ingredients used or is an additive derived from the product of decaffeination or from chemical synthesis. Guarana, a prime ingredient of energy drinks, contains large amounts of caffeine with small amounts of theobromine and theophylline in a naturally occurring slow-release excipient.[11]

History of use

Humans have consumed caffeine since the Stone Age.[12] Early peoples found that chewing the seeds, bark, or leaves of certain plants had the effects of easing fatigue, stimulating awareness, and elevating mood. Only much later was it found that the effect of caffeine was increased by steeping such plants in hot water. Many cultures have legends that attribute the discovery of such plants to people living many thousands of years ago.

According to one popular Mongolian legend, the Emperor of China Shennong, reputed to have reigned in about 3,000 BC, accidentally discovered that when some leaves fell into boiling water, a fragrant and restorative drink resulted.[13] Shennong is also mentioned in Lu Yu's Cha Jing, a famous early work on the subject of tea.[14]

The early history of coffee is obscure, but a popular myth traces its discovery to Ethiopia, where Coffea arabica originates. According to this myth, a goatherder named Kaldi observed goats that became elated and sleepless at night after browsing on coffee shrubs and, upon trying the berries that the goats had been eating, experienced the same vitality. The earliest literary mention of coffee may be a reference to Bunchum in the works of the 9th century Persian physician al-Razi. In 1587, Malaye Jaziri compiled a work tracing the history and legal controversies of coffee, entitled "Umdat al safwa fi hill al-qahwa". In this work, Jaziri recorded that one Sheikh, Jamal-al-Din al-Dhabhani, mufti of Aden, was the first to adopt the

use of coffee in 1454, and that in the 15th century the Sufis of Yemen routinely used coffee to stay awake during prayers.

Towards the close of the 16th century, the use of coffee was recorded by a European resident in Egypt, and about this time it came into general use in the Near East. The appreciation of coffee as a beverage in Europe, where it was first known as "Arabian wine," dates from the 17th century. During this time "coffee houses" were established, the first being opened in Constantinople and Venice. In Britain, the first coffee houses were opened in London in 1652, at St Michael's Alley, Cornhill. They soon became popular throughout Western Europe, and played a significant role in social relations in the 17th and 18th centuries.[15]

The kola nut, like the coffee berry and tea leaf, appears to have ancient origins. It is chewed in many West African cultures, individually or in a social setting, to restore vitality and ease hunger pangs. In 1911, kola became the focus of one of the earliest documented health scares when the US government seized 40 barrels and 20 kegs of Coca-Cola syrup in Chattanooga, Tennessee, alleging that the caffeine in its drink was "injurious to health".[16] On March 13, 1911, the government initiated The United States vs. Forty Barrels and Twenty Kegs of Coca-Cola, hoping to force Coca-Cola to remove caffeine from its formula by making exaggerated claims, such as that the excessive use of Coca-Cola at one girls' school led to "wild nocturnal freaks, violations of college rules and female proprieties, and even immoralities."[17] Although the judge ruled in favor of Coca-Cola, two bills were introduced to the U.S. House of Representatives in 1912 to amend the Pure Food and Drug Act, adding caffeine to the list of "habit-forming" and "deleterious" substances which must be listed on a product's label.

The earliest evidence of cocoa use comes from residue found in an ancient Mayan pot dated to 600 BC. In the New World, chocolate was consumed in a bitter and spicy drink called xocoatl, often seasoned with vanilla, chile pepper, and achiote. Xocoatl was believed to fight fatigue, a belief that is probably attributable to the theobromine and caffeine content. Chocolate was an important luxury good throughout pre-Columbian Mesoamerica, and cocoa beans were often used as currency.

Chocolate was introduced to Europe by the Spaniards and became a popular beverage by 1700. They also introduced the cacao tree into the West Indies and the Philippines. It was used in alchemical processes, where it was known as Black Bean.

The first coffee house in Europe was opened Paris in the 1800's by an French-Armenian named Pascal. Armenian merchants played in role in the more modern history of coffee and this is the reason why the coffee growing region in is named the Armenia Region of Columbia.

In 1819, the German chemist Friedrich Ferdinand Runge isolated relatively pure caffeine for the first time. According to a legend, he did this at the behest of Johann Wolfgang von Goethe.[18]

Today, global consumption of caffeine has been estimated at 120,000 tons per annum,[19] making it the world's most popular psychoactive substance. This number equates to one serving of a caffeinic beverage for every person, per day. In North America, 90% of adults consume some amount of caffeine daily.

Effects

Caffeine is a central nervous system and metabolic stimulant,[20] and is used both recreationally and medically to reduce physical fatigue and restore mental alertness when unusual weakness or drowsiness occurs. Caffeine stimulates the central nervous system first at the higher levels, resulting in increased alertness and wakefulness, faster and clearer flow of thought, increased focus, and better general body coordination, and later at the spinal cord level at higher doses.[21] The precise amount of caffeine necessary to produce effects varies from person to person depending on body size and degree of tolerance to caffeine. It takes less than an hour for caffeine to begin affecting the body and a mild dose wears off in three to four hours.[21] Consumption of caffeine does not eliminate the need for sleep: it only temporarily reduces the sensation of being tired.

With these effects, caffeine is an ergogenic: increasing the capacity for mental or physical labor. A study conducted in 1979 showed a 7% increase in distance cycled over a period of two hours in subjects who consumed caffeine compared to control tests.[22] Other studies attained much more dramatic results; one particular study of trained runners showed a 44% increase in "race-pace" endurance, as well as a 51% increase in cycling endurance, after a dosage of 9 milligrams of caffeine per kilogram of body weight.[23] The extensive boost shown in the runners is not an isolated case; additional studies have reported similar effects. Another study found 5.5 milligrams of caffeine per kilogram of body mass resulted in subjects cycling 29% longer during high intensity circuits.[24]

Caffeine is sometimes administered in combination with medicines to increase their effectiveness. Caffeine makes pain relievers 40% more effective in relieving headaches and helps the body absorb headache medications more quickly, bringing faster relief.[25] For this reason, many over-the-counter headache drugs include caffeine in their formula. It is also used with ergotamine in the treatment of migraine and cluster headaches as well as to overcome the drowsiness caused by antihistamines.

Breathing problems in premature infants, apnea of prematurity, are sometimes treated with citrated caffeine, which is available only by prescription in many countries.[26] A reduction in bronchopulmonary dysplasia has been exhibited in premature infants treated with caffeine citrate therapy regimens. It is speculated that this reduction in bronchopulmonary dysplasia is tied to a reduction in exposure to positive airway pressure. The only short term risk associated with this treatment is a temporary reduction in weight gain during the therapy.[27]

While relatively safe for humans, caffeine is considerably more toxic to some other animals such as dogs, horses and parrots due to a much poorer ability to metabolize this compound. Caffeine has a much more significant effect on spiders, for example, than most other drugs do.[28]

Overuse

Caffeine is a drug that in large amounts, especially over an extended period of time, can lead to a condition termed "caffeinism." Caffeinism usually combines physical addiction with a wide range of unpleasant physical and mental conditions including nervousness, irritability, anxiety, tremulousness, muscle twitching (hyperreflexia), insomnia, and heart palpitations.[29] (Under a rigid definition of addiction, meaning a process of escalating use,

"caffeine dependency" would be a more descriptive term. However, under the widely accepted definition "chronic pattern of behavior that is perceived to be difficult to quit," caffeine may be said to be addictive.) Furthermore, because caffeine increases the production of stomach acid, high usage over time can lead to peptic ulcers, erosive esophagitis, and gastroesophageal reflux disease.[30] However, since both "regular" and decaffeinated coffees have also been shown to stimulate the gastric mucosa and increase stomach acid secretion, caffeine is probably not the only component of coffee responsible.[31]

There are four caffeine-induced psychiatric disorders recognized by the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition: caffeine intoxication, caffeine-induced anxiety disorder, caffeine-induced sleep disorder, and caffeine-related disorder not otherwise specified (NOS).

Caffeine intoxication

An acute overdose of caffeine, usually in excess of 250 milligrams (more than 2-3 cups of brewed coffee), can result in a state of central nervous system overstimulation called caffeine intoxication. The symptoms of caffeine intoxication may include restlessness, nervousness, excitement, insomnia, flushing of the face, increased urination, gastrointestinal disturbance, muscle twitching, a rambling flow of thought and speech, irregular or rapid heart beat, and psychomotor agitation.[29][32]

In cases of extreme overdose, death can result. The median lethal dose (LD50) of caffeine is 192 milligrams per kilogram in rats.[33] The LD50 of caffeine is dependent on weight and individual sensitivity and estimated to be about 150 to 200 milligrams per kilogram of body mass, roughly 140 to 180 cups of coffee for an average adult taken within a limited timeframe that is dependent on half-life. Though achieving lethal dose with caffeine would be exceptionally difficult with regular coffee, there have been reported deaths from overdosing on caffeine pills.[34][35][36][37]

Treatment of severe caffeine intoxication is generally supportive, providing treatment of the immediate symptoms, but if the patient has very high serum levels of caffeine then peritoneal dialysis, hemodialysis, or hemofiltration may be required.

Anxiety and sleep disorders

Long-term overuse of caffeine can elicit a number of psychiatric disturbances. Two such disorders recognized by the APA are caffeine-induced sleep disorder and caffeine-induced anxiety disorder.

In the case of caffeine-induced sleep disorder, an individual regularly ingests high doses of caffeine sufficient to induce a significant disturbance in his or her sleep, sufficiently severe to warrant clinical attention.[38]

In some individuals, the large amounts of caffeine can induce anxiety severe enough to necessitate clinical attention. This caffeine-induced anxiety disorder can take many forms, from generalized anxiety, to panic attacks, obsessive-compulsive symptoms, or even phobic

symptoms.[38] Because this condition can mimic organic mental disorders, such as panic disorder, generalized anxiety disorder, bipolar disorder, or even schizophrenia, a number of medical professionals believe caffeine-intoxicated people are routinely misdiagnosed and unnecessarily medicated when the treatment for caffeine-induced psychosis would simply be to withhold further caffeine.[39] A Study in the British Journal of Addiction concluded that caffeinism, although infrequently diagnosed, may afflict as many as one person in ten of the population.[40]

Pharmacology

Metabolism

Caffeine is completely absorbed by the stomach and small intestine within 45 minutes of ingestion. After ingestion it is distributed throughout all tissues of the body and is eliminated by first-order kinetics.[41]

The half-life of caffeine — the time required for the body to eliminate one-half of the total amount of caffeine consumed at a given time — varies widely among individuals according to such factors as age, liver function, pregnancy, some concurrent medications, and the level of enzymes in the liver needed for caffeine metabolism. In healthy adults, caffeine's half-life is approximately 3-4 hours. In women taking oral contraceptives this is increased to 5-10 hours,[42] and in pregnant women the half-life is roughly 9-11 hours.[43] Caffeine can accumulate in individuals with severe liver disease when its half-life can increase to 96 hours.[44] In infants and young children, the half-life may be longer than in adults; half-life in a newborn baby may be as long as 30 hours. Other factors such as smoking can shorten caffeine's half-life.[45]

Caffeine is metabolized in the liver by the cytochrome P450 oxidase enzyme system (specifically, the 1A2 isozyme) into three metabolic dimethylxanthines,[46] which each have their own effects on the body:

- Paraxanthine (84%) – Has the effect of increasing lipolysis, leading to elevated glycerol and free fatty acid levels in the blood plasma.
- Theobromine (12%) – Dilates blood vessels and increases urine volume. Theobromine is also the principal alkaloid in cocoa, and therefore chocolate.
- Theophylline (4%) – Relaxes smooth muscles of the bronchi, and is used to treat asthma. The therapeutic dose of theophylline, however, is many times greater than the levels attained from caffeine metabolism.

Each of these metabolites is further metabolized and then excreted in the urine.

Mechanism of action

Caffeine acts through multiple mechanisms involving both action on receptors and channels at the cell membrane, as well as intracellular action on Calcium and cAMP pathways. By virtue of its purine structure it can act on some of the same targets as adenosine related nucleosides and nucleotides, like the cell surface P1 GPCRs for adenosine, as well as

the intracellular Ryanodine receptor which is the physiological target of cADPR (cyclic ADP ribose), and cAMP-phosphodiesterase (cAMP-PDE). However the action is antagonistic in some cases and agonistic in some others.

The principal mode of action of caffeine is as an antagonist of adenosine receptors in the brain.[47] The caffeine molecule is structurally similar to adenosine, and binds to adenosine receptors on the surface of cells without activating them (a "false transmitter" method of antagonism). The reduction in adenosine activity results in increased activity of the neurotransmitter dopamine, largely accounting for the stimulatory effects of caffeine. Caffeine can also increase levels of epinephrine/adrenaline,[48] possibly via a different mechanism. Acute usage of caffeine also increases levels of serotonin, causing positive changes in mood.

The inhibition of adenosine may be relevant in its diuretic properties. Because adenosine is known to constrict preferentially the afferent arterioles of the glomerulus, its inhibition may cause vasodilation, with an increase in renal blood flow (RBF) and glomerular filtration rate (GFR). This effect, called competitive inhibition, interrupts a pathway that normally serves to regulate nerve conduction by suppressing post-synaptic potentials. The result is an increase in the levels of epinephrine and norepinephrine/noradrenaline released via the hypothalamic-pituitary-adrenal axis.[49] Epinephrine, the natural endocrine response to a perceived threat, stimulates the sympathetic nervous system, leading to an increased heart rate, blood pressure and blood flow to muscles, a decreased blood flow to the skin and inner organs and a release of glucose by the liver.

Caffeine is also a known competitive inhibitor of the enzyme cAMP-phosphodiesterase (cAMP-PDE), which converts cyclic AMP (cAMP) in cells to its noncyclic form, allowing cAMP to build up in cells. Cyclic AMP participates in the messaging cascade produced by cells in response to stimulation by epinephrine, so by blocking its removal caffeine intensifies and prolongs the effects of epinephrine and epinephrine-like drugs such as amphetamine, methamphetamine, or methylphenidate. Increased concentrations of cAMP in parietal cells causes an increased activation of protein kinase A (PKA) which in turn increases activation of H^+/K^+ ATPase, resulting finally in increased gastric acid secretion by the cell.

Caffeine (and theophylline) can freely diffuse into cells and causes intracellular calcium release (independent of extracellular calcium) from the calcium stores in the Endoplasmic Reticulum(ER). This release is only partially blocked by Ryanodine receptor blockade with ryanodine, dantrolene, ruthenium red, and procaine (thus may involve ryanodine receptor and probably some additional calcium channels), but completely abolished after calcium depletion of ER by SERCA inhibitors like Thapsigargin (TG) or cyclopiazonic acid (CPA).[50] The action of caffeine on the ryanodine receptor may depend on both cytosolic and the luminal ER concentrations of Ca^{2+}. At low millimolar concentration of caffeine, the RyR channel open probability (Po) is significantly increased mostly due to a shortening of the lifetime of the closed state. At concentrations >5 mM, caffeine opens RyRs even at picomolar cytosolic Ca^{2+} and dramatically increases the open time of the channel so that the calcium release is stronger than even an action potential can generate. This mode of action of caffeine is probably due to mimicking the action of the physiologic metabolite of NAD called cADPR (cyclic ADP ribose) which has a similar potentiating action on Ryanodine receptors.

Caffeine may also directly inhibit delayed rectifier and A-type K^+ currents and activate plasmalemmal Ca^{2+} influx in certain vertebrate and invertebrate neurons.

The metabolites of caffeine contribute to caffeine's effects. Theobromine is a vasodilator that increases the amount of oxygen and nutrient flow to the brain and muscles. Theophylline, the second of the three primary metabolites, acts as a smooth muscle relaxant that chiefly affects bronchioles and acts as a chronotrope and inotrope that increases heart rate and efficiency. The third metabolic derivative, paraxanthine, is responsible for an increase in the lipolysis process, which releases glycerol and fatty acids into the blood to be used as a source of fuel by the muscles.[51]

Tolerance and withdrawal

Because caffeine is primarily an antagonist of the central nervous system's receptors for the neurotransmitter adenosine, the bodies of individuals who regularly consume caffeine adapt to the continual presence of the drug by substantially increasing the number of adenosine receptors in the central nervous system. This increase in the number of the adenosine receptors makes the body much more sensitive to adenosine, with two primary consequences.[52] First, the stimulatory effects of caffeine are substantially reduced, a phenomenon known as a tolerance adaptation. Second, because these adaptive responses to caffeine make individuals much more sensitive to adenosine, a reduction in caffeine intake will effectively increase the normal physiological effects of adenosine, resulting in unwelcome withdrawal symptoms in tolerant users.[52]

Because adenosine, in part, serves to regulate blood pressure by causing vasodilation, the increased effects of adenosine cause the blood vessels of the head to dilate, leading to an excess of blood in the head and causing a headache and nausea. Reduced catecholamine activity may cause feelings of fatigue and drowsiness. A reduction in serotonin levels when caffeine use is stopped can cause anxiety, irritability, inability to concentrate and diminished motivation to initiate or to complete daily tasks; in extreme cases it may cause mild depression.

Withdrawal symptoms — possibly including headache, irritability, and an inability to concentrate — may appear within 12 to 24 hours after discontinuation of caffeine intake, peak at roughly 48 hours, and usually last from one to five days - representing the time required for the number of adenosine receptors in the brain to revert to "normal" levels, uninfluenced by caffeine consumption. Analgesics, such as aspirin, can relieve the pain symptoms, as can a small dose of caffeine.[53] Most effective is a combination of both an analgesic and a small amount of caffeine.

Currently caffeine withdrawal is recognized as meriting further study by the Diagnostic and Statistical Manual of Mental Disorders for DSM-IV, although research demonstrating its clinical significance means that it will likely be included as an Axis-1 disorder in the DSM-V.[54]

Extraction of pure caffeine

Caffeine extraction is an important industrial process and can be performed using a number of different solvents. Benzene, chloroform, trichloroethylene and dichloromethane

have all been used over the years but for reasons of safety, environmental impact, cost and flavor, they have been superseded by the following main methods:

Water extraction

Coffee beans are soaked in water. The water, which contains not only caffeine but also many other compounds which contribute to the flavor of coffee, is then passed through activated charcoal, which removes the caffeine. The water can then be put back with the beans and evaporated dry, leaving decaffeinated coffee with a good flavor.[55] Coffee manufacturers recover the caffeine and resell it for use in soft drinks and medicines.

Supercritical carbon dioxide extraction

Supercritical carbon dioxide is an excellent nonpolar solvent for caffeine (as well as many other organic compounds), and is safer than the organic solvents that are used for caffeine extraction. The extraction process is simple: CO2 is forced through the green coffee beans at temperatures above 31.1 °C and pressures above 73 atm. Under these conditions, CO2 is in a "supercritical" state: it has gaslike properties which allow it to penetrate deep into the beans but also liquid-like properties which dissolve 97-99% of the caffeine. The caffeine-laden CO2 is then sprayed with high pressure water to remove the caffeine. The caffeine can then be isolated by charcoal adsorption (as above) or by distillation, recrystallization, or reverse osmosis.[55]

Extraction by nonhazardous organic solvents

Organic solvents such as ethyl acetate present much less health and environmental hazard than previously used chlorinated and aromatic solvents. The hydrolysis products of ethyl acetate are ethanol and acetic acid, both nonhazardous in small quantities. Another method is to use triglyceride oils obtained from spent coffee grounds.

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Appendix

Relative content: comparison of different sources

Caffeine equivalents

In general, each of the following contains approximately 200 milligrams of caffeine:

- *One* 200 milligram caffeine pill
- *One and one quarter* 16 fluid ounce cans of Monster Energy (590 millilitres)
- *One and a half* pounds of milk chocolate (680 grams)
- *Two* 8 fluid ounce containers of regular coffee (470 millilitres)
- *Two and a half* 10 oz. bottles of Bawls caffeinated drink (740 millilitres)
- *Three* standard Excedrin pills
- *Three* 8 fluid ounce cups of Red Bull energy drink (710 millilitres)
- *Four* 8 fluid ounce cups of Vault energy drink (1.0 litre)
- *Five* 1 fluid ounce shots of espresso from robusta beans (150 millilitres)
- *Five* 8 fluid ounce cups of black tea (1.2 litres)
- *Five* 8 fluid ounce cups of Mountain Dew (1.2 litres)
- *Five* 12 fluid ounce cans of typical soda pop (1.8 litres) (variable)
- *Eight and a half* 8 fluid ounce cups of Coca-Cola Classic (2.0 litres)
- *Ten* 8 fluid ounce cups of green tea (2.4 litres)
- *Fifty* 8 fluid ounce cups of decaffeinated coffee (12 litres)

Coffee

Coffee is a popular beverage prepared from the roasted seeds – commonly referred to as beans – of the coffee plant. It is usually served hot but can also be served cold. A typical 7 fluid ounce (ca. 207 mL) cup of coffee contains 80-140 milligrams of caffeine, depending on the method of preparation.[1] Coffee represents 71% of all the United States caffeine consumption followed by soft drinks and tea.[2] Coffee, along with tea and water, is one of the most frequently-drunk beverages, its volume amounting to about a third that of tap water.[3] In 2003, coffee was the world's sixth largest agricultural export in terms of value, behind wheat, maize, soybeans, palm oil and sugar.[4]

Etymology and history

The history of coffee begins in the 9th century. It originated in the highlands of Ethiopia and spread to the rest of the world via Egypt and Europe.[5] The word coffee is believed to be derived from the word Kaffa, a region in Ethiopia where coffee originated. Later through its expansion, the name later evolved into Arabic word BGH) Qah'wa, over Ottoman Turkish Kahve, which originally meant wine or other intoxicating liquors. In the 15th century, Muslims introduced coffee in Persia, Egypt, northern Africa and Turkey, where the first coffeehouse, Kiva Han, opened in 1475 in Constantinople. The stimulant effect of drinking coffee caused it to be forbidden among orthodox and conservative imams in Mecca in 1511 and in Cairo in 1532 by a theological court. In Egypt, coffeehouses and warehouses containing coffee cherries were sacked. But the product's popularity, particularly among

intellectuals, led to the reversal of this decision in 1524 by an order of the Ottoman Turkish Sultan Selim I.[6]

From the Muslim world, coffee spread to Europe, where it became popular in the 17th century. Dutch traders were the first to start the large scale importation of coffee into Europe. In 1538, Léonard Rauwolf, a German physician, having come back from a ten-year trip in the Near East, was the first westerner to describe the brew:[7]

"A beverage as black as ink, useful against numerous illnesses, particularly those of the stomach. Its consumers take it in the morning, quite frankly, in a porcelain cup that is passed around and from which each one drinks a cupful. It is composed of water and the fruit from a bush called bunnu."

These remarks were noted by merchants, who were sensitive to this kind of information through experience in the commerce of spices. English coffeehouses were centers of intellectual and commercial activity. Lloyds of London, the famous insurance firm, was originally a coffeehouse.[8]

Coffee seed types

There are two main species of the *coffee plant*, Coffea arabica being the older one. Coffee is thought to be indigenous to south-western Ethiopia, specifically from Kaffa, from which it may have acquired its name.[9] While more susceptible to disease, it is considered by most to taste better than the second species, Coffea canephora (robusta). Robusta, which contains about 40-50% more caffeine, can be cultivated in environments where arabica will not thrive and probably originated in Uganda.[9] This has led to its use as an inexpensive substitute for arabica in many commercial coffee blends. Compared to arabica, robusta tends to be bitter and has little flavor, with a telltale "burnt rubber" or "wet cardboard" aroma and flavor. Good quality robustas are used in some espresso blends to provide a better "crema" (foamy head), and to lower the ingredient cost. In Italy, many espresso blends are based on dark-roasted robusta. The large industrial roasters use a steam treatment process to remove undesirable flavors from robusta beans for use in mass-marketed coffee blends.[10] Other species include Coffea liberica and Coffea esliaca, believed to be indigenous to Liberia and southern Sudan respectively.[9]

Arabica coffees were traditionally named by the port they were exported from, the two oldest being Mocha, from Yemen, and Java, from Indonesia. The modern coffee trade is much more specific about origin, labeling coffees by country, region, and sometimes even the producing estate. Varietal[11] is a botanical term denoting a taxonomic category ranking below species, a designation more specific than arabica or robusta and unrelated to the coffee's place of origin. Coffees consisting entirely of beans from a single varietal, bourbon, for example, are generally referred to as such, along with a reference to their place of origin (as in: Rwanda Blue Bourbon). Coffee aficionados may even distinguish auctioned coffees by lot number.

Most arabica coffee beans originate from one of three growing regions; Central America, East Africa/Arabia and Asia/Pacific. Beans from different countries or regions usually have distinctive characteristics such as flavor (flavor criteria include terms such as "citrus-like" or "earthy"), aroma (sometimes "berry-like" or "flowery"), body or mouthfeel, and acidity. Acidity refers to a tangy or clean-tasting quality, typically present in washed or wet processed coffees. It does not refer to a coffee's pH level. (Black coffee has a pH of around 5).[12] These distinguishing taste characteristics are dependent not only on the coffee's growing region, but also on its method of process and genetic subspecies or varietal.[13]

A peaberry, (also sometimes called a "Caracoli" bean) is a coffee bean that that develops singly inside the coffee cherry instead of the usual pair of beans. This situation occurs 5-10% of the time. Since flavour is concentrated when only a single bean is grown inside the cherry, these beans (especially Arabica) are highly prized.[14]

Processing and roasting

Much processing and human labour is required before coffee berries and its seed can be processed into the roasted coffee with which most Western consumers are familiar. Coffee berries must be picked, defruited, dried, sorted, and—in some processes—also aged.

Coffee is usually sold roasted, and the roasting process has a great degree of influence on the taste of the final product. All coffee is roasted before being consumed. Coffee can be sold roasted by the supplier; alternatively it can be home roasted.

Everyday alchemy, coffee roasting coaxes golden flavor from a bland bean. Unroasted beans boast all of coffee's acids, protein, and caffeine—but none of its taste. It takes heat to spark the chemical reactions that turn carbohydrates and fats into aromatic oils, burn off moisture and carbon dioxide, and alternately break down and build up acids, unlocking the characteristic coffee flavor.

Preparation

The processing of coffee typically refers to the agricultural and industrial processes needed to deliver whole roasted coffee beans to the consumer. Grinding the roasted coffee beans is done at a roastery, in a grocery store, or at home. It is most commonly ground at the roastery and sold to the consumer ground and packaged, though "whole-bean" coffee that is ground at home is becoming more popular despite the extra effort required. A grind is referred to by its brewing method. "Turkish" grind, the finest, is meant for mixing straight with water, while the coarsest grinds, such as coffee percolator or French press, are at the other extreme. Midway between the extremes are the most common: "drip" and "paper filter" grinds, which are used in the most common home coffee brewing machines. The "drip" machines operate with near-boiling water passed in a slow stream through the ground coffee in a paper filter. The espresso method uses more advanced technology to force very hot (not boiling) water, through the ground coffee, resulting in a stronger flavor and chemical changes with more coffee bean matter in the drink. Once brewed, it may be presented in a variety of ways: on its own, with sugar, with milk or cream, hot or cold, and so on. Roasted arabica beans are also eaten plain and covered with chocolate. See the article on coffee preparation for a comprehensive list.

A number of products are sold for the convenience of consumers who don't want to prepare their own coffee. Instant coffee has been dried into soluble powder or freeze dried into granules, which can be quickly dissolved in hot water for consumption. Canned coffee is a beverage that has been popular in Asian countries for many years, particularly in Japan and South Korea. Vending machines typically sell a number of varieties of canned coffee, available both hot and cold. To match the often busy life of Korean city dwellers, companies mostly have canned coffee with a wide variety of tastes. Japanese convenience stores and groceries also have a wide availability of plastic-bottled coffee drinks, which are typically lightly sweetened and pre-blended with milk. Lastly, liquid coffee concentrate is sometimes used in large institutional situations where coffee needs to be produced for thousands of people at the same time. It is described as having a flavor about as good as low-grade robusta coffee, and costs about 10 cents a cup to produce. The machines used to process it can handle up to 500 cups an hour, or 1,000 if the water is preheated.[15]

Economics of coffee

Coffee is one of the world's most important primary commodities due to being one of the world's most popular beverages. In total, 6.7 million tonnes of coffee were produced

annually in 1998-2000, and the forecast is a rise to 7 million tonnes annually by 2010.[16] Coffee also has several types of classifications used to determine environmental and labor standards.

Brazil remains the largest coffee exporting nation, but in recent years the green coffee market has been flooded by large quantities of robusta beans from Vietnam.[17] Many experts believe the giant influx of cheap green coffee after the collapse of the International Coffee Agreement of 1975-1989 with Cold War pressures led to the prolonged pricing crisis from 2001 to 2004.[18] In 1997 the "c" price of coffee in New York broke US$3.00/lb, but by late 2001 it had fallen to US$0.43/lb. Robusta coffees (traded in London at much lower prices than New York's Arabica) are preferred by large industrial clients (multinational roasters, instant coffee producers, etc.) because of their lower cost.

The preference of the "Big Four" coffee companies for cheap robusta is believed by many to have been a major contributing factor to the crash in coffee prices,[19] and the demand for high-quality arabica beans is only slowly recovering. After the crash, many coffee farmers in Africa, Indonesia and South and Central America lost their livelihoods, or turned to illicit crops such as coca to earn a living. The Dutch brand 'Max Havelaar' started the concept of fair trade Labelling, which attempted to remedy the situation by guaranteeing coffee growers a negotiated pre-harvest price; many smaller roasters and recently Procter & Gamble and Starbucks have joined Fair Trade.[20] Another issue with coffee is ecological: the American Birding Association has led a campaign for sustainably harvested, shade-grown and organic coffees vs. the newer mono-cropped full-sun varieties, which lead to deforestation and loss of bird habitat.[21]

Coffee ingestion on average is about a third that of tap water in most of North America and Europe.[3] In 2002 in the US, coffee consumption was 22.1 gallons per person.[22]

Health and pharmacology of coffee

Many studies have been performed on the relationship between coffee consumption and many medical conditions, ranging from diabetes and cardiovascular disease to cancer and cirrhosis. Studies are contradictory as to whether coffee has any specific health benefits, and results are similarly conflicting with respect to negative effects of coffee consumption.[23] In addition, it is often unclear whether these risks or benefits are linked to caffeine or whether they are to be attributed to other chemical substances found in coffee (and whether decaffeinated coffee carries the same benefits or risks).

One fairly consistent finding has been the reduction of diabetes mellitus type 2 in coffee consumers, an association that cannot be explained by the caffeine content alone and indeed may be stronger in decaffeinated coffee.[24]

Recently, coffee was found to reduce the chances of developing cirrhosis of the liver: the consumption of 1 cup a day was found to reduce the chances by 20%, and 4 cups a day reduced the chances by 80%.[25]

Social aspects of coffee

Coffee plays an important role in many societies throughout the world today. From the coffeehouses of the 16th century, to the modern day cafés, coffee has had a profound impact

on the lifestyles of people from all walks of life. When it first appeared in Africa and Yemen, it was commonly used as a type of religious intoxicant. This usage in religious rites among the Sufi branch of Islam led to it being put on trial in Mecca for being a "heretic" substance much as wine was. It was briefly repressed at this point, and was later part of a larger ban in Ottoman Turkey under an edict that led to the death of thousands of people.[26] Its early association in Europe with rebellious political activities led to its banning in England, among other places.[27]

In India the Indian Coffee Houses became an icon of the worker's struggle. This restaurant chain is now owned by the workers of ICHs, as a result of the struggle performed by the thrown-out workers from the Coffee Houses of Coffee Board. This struggle was led by famed Communist leader of India A. K. Gopalan. Thus the ICHs became the meeting places of the progressive-minded in India later.

Other uses

Spent coffee grounds are a good fertilizer in gardens because of their high nitrogen content. Starbucks, and some other coffee shops, have a specific policy of giving away their used coffee grounds to gardeners. While they tend to be only slightly acidic, they also tend to improve the acidity of garden soil through the same chemical processes that make sawdust a good fertilizer. Coffee grounds raise soil acidity sooner if they are added fresh, instead of after brewing. Likewise, coffee diluted with four times its volume of water can be used to amend soil acidity, especially useful for tomatoes, chili peppers, blueberries, and other plants that like high soil acidity.

The grounds are also used as bait in "Vegas roach traps".

Some use coffee to create art. Latte art involves designs in the foam of espresso-based drinks. Arfé is the use of coffee as a coloring for painting or other visual effects.

See also

- Tea

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Hard and soft drugs

Hard and soft drugs are loose categories of psychoactive drugs. This distinction is used in both official and casual discourse. The term *hard drug* generally refers to drugs illegal for nonmedical use that lead to profound and severe addiction, as opposed to *soft drugs* that are either only mildly psychologically addictive or non-addictive.

Hard drugs

Cocaine (in powder form or in smokable form as crack), the Amphetamine, and the opioids such as heroin and morphine, are most commonly referred to as hard drugs. According to researchers, medical evidence indicates that alcohol and nicotine, while freely available for sale in many countries, should be described as hard drugs as well because they

are both addictive, associated with high mortality rates, and cause significantly more damage to the body than virtually all illegal drugs when compared scientifically (for example pharmaceutically pure or even reasonably purified street heroin, when consumed following a few basic safety rules, actually causes no harm to the body, even when taken over years or decades, while alcohol use is associated with liver and brain damage but is only age-restricted). In most popular discourse, however, hard drugs refers to drugs illegal for nonmedical use associated with highly visible problematic users, in the United Kingdom these are predominantly heroin, cocaine, and methamphetamine.

Soft drugs

The term soft drug is most usually applied to cannabis (marijuana or hashish) because it is not associated with deaths, crime or violence amongst users and is without evidence of physical addiction. This distinction between soft drugs and hard drugs is important in the drug policy of the Netherlands, where cannabis production, retailing and use come under official tolerance (NL gedoogbeleid), subject to certain conditions. Other psychedelic drugs such as psilocybin and LSD are also considered soft drugs by many because there is no evidence of physical addiction and it is nearly impossible to overdose on these drugs. There have been no human deaths recorded from the use of psychedelics (with the exception of MDMA, which has produced no overdoses).

Hallucinogens

Some consider certain hallucinogens to be hard drugs, but as most hallucinogens are non-addictive, nor are they known for causing deaths, such drugs generally occupy a middle ground - neither hard nor soft. The possible exceptions are PCP, DXM and the phenethylamine-based empathogens such as MDMA, many of which are closely related to amphetamines; being relatively new to the drug culture more research is needed to ascertain the addictive potential and potential harms of these drugs.

The drug policy of the Netherlands classifies synthetic hallucinogens such as LSD (acid) and MDMA (ecstasy) as hard drugs, although they have very similar action to naturally occurring drugs such as mescaline, which is considered a soft drug in its natural form of peyote, or psilocybin in its natural form as psilocybe (magic mushrooms). Both are sold legally in the Netherlands in their unprocessed natural form.

Psychopharmacology

Psychopharmacology is the study of drug-induced changes in mood, thinking, and behavior.[1] These drugs may originate from plants, minerals, synthetic/chemical, or herbal derivatives or animal by-products. Changes in mood, thinking, and behavior may be mediated by interaction of these drugs with particular target sites or receptors found in the nervous system. For example, the increase in locomotor behavior and schedule-controlled

behaviors following the acute administration of cocaine is often attributed to the drug's ability to inhibit the reuptake of the neutransmitter, dopamine, into the nerve terminal.

The common muscimol-bearing mushroom Amanita muscaria, also known as the Fly Agaric, is frequently regarded as one of the first used psychoactive drugs, it is suspected to be the primary/active ingredient in the sacred drug of ancient India, known as Soma. There are many modern theories citing the discovery of its psychoactive properties as far back as 10,000 BCE. Modern *psychopharmacology* studies a wide range of substances with various types of psychoactive properties, though the professional and commercial fields of pharmacology/*psychopharmacology* don't typically focus on psychedelic or recreational drugs, the majority of studies are conducted on medicinal psychoactives. Bar none, studies are conducted on *all* psychoactives by both fields, *psychopharmacology* focuses primarily on the psychoactive and chemical interactions with the brain.

History

Psychoactive drug use predates recorded history. Hunter-gatherer societies tended to favor hallucinogenic drugs, and today their use can still be observed in many surviving tribal cultures. The exact drug used depends on what the particular ecosystem a given tribe lives in can support, and are typically found growing wild. Such drugs include various hallucinogenic mushrooms and cacti, along with many other plants. These societies generally attach spiritual significance to drug use, and often incorporate it into their religious practices.

With the dawn of the Neolithic and the proliferation of agriculture, new entheogens came into use as a natural by-product of farming. Among them were opium, cannabis, and alcohol derived from the fermentation of cereals and fruits. Most societies began developing herblores, lists of herbs which were good for treating various physical and mental ailments. For example, St. John's Wort was traditionally prescribed in Europe for depression (in addition to use as a general-purpose good-tasting tea), and Chinese medicine developed elaborate lists of herbs and preparations.

With the scientific revolution in Europe and America, the use of traditional herbal remedies fell out of favor with the mainstream medical establishment, although a few people continued to use and maintain knowledge of traditional European herblore. In the early 20th century, scientists began reassessing this rejection of traditional herbs in medicine. A number of important psychiatric drugs have been developed as a byproduct of the analysis of organic compounds present in traditional herbal remedies. The use of psychiatric drugs to restore mental health, or at least limit aberrant behaviour, has only been part of the European and American medical institution since the 1950s, when a number of new classes of drugs were discovered, notably tranquillizers and antidepressants, and LSD was popularized among many psychiatrists as a mental miracle drug capable of curing all manner of problems.

In the latter half of the 20th century, research into new psychopharmacologic drugs exploded, with many new drugs discovered, created, and tested. Many once-popular drugs are now out of favor, and there are fashions in psychiatric drugs, as with any other kind of drug.

Major Drug Classes that are Studied

Psychopharmacology studies a very wide array of drugs, ranging from antidepressants to stimulants. Drugs are researched for their pharmaceutical properties, physical side effects, and psychological side effects. These studies are often very specific, typically beginning with animal testing, and ending with human testing. In the human testing phase, there is often a group of subjects, one group is given a placebo, and the other is administered a carefully measured therapeutic dose of the drug in question. After all of the testing is completed, the drug is proposed to the FDA, and is either commercially introduced to the public, introduced to the public via prescription, or deemed safe enough for over the counter sale.

Antipsychotics

Main article: Antipsychotics

Antipsychotics are drugs that are used in the treatment of various symptoms of psychosis, such as those caused by Psychotic Disorders or Schizophrenia. Antipsychotics are also sometimes used as mood stabilizers, most frequently to help manage such disorders as Bipolar disorder, even if no symptoms of psychosis are present. Antipsychotics may also be referred to as *neuroleptic drugs* and some antipsychotics are branded as *major tranquilizers*.

There are two categories of Antipsychotics, typical antipsychotics and atypical antipsychotics, and due to the nature of the drugs the majority of them require a verifiable prescription from a licensed professional.

Common Antipsychotics:

- Chlorpromazine HCl (Thorazine®), Typical antipsychotic
- Thioridazine HCl (Mellaril®), Typical antipsychotic
- Haloperidol **(Haldol®),** Typical antipsychotic
- Perphenazine (Trilafon®), Typical antipsychotic
- Thiothixene (Navane®), Typical antipsychotic
- Trifluoperazine HCl (Stelazine®), Typical antipsychotic
- Risperidone (Belivon®, Rispen®, Risperdal®), Atypical antipsychotic
- Quetiapine (Seroquel®), Atypical antipsychotic

Antidepressants

Main article: Antidepressants

Antidepressants are drugs used in the treatment of clinical depression, and are often used in combination with other drugs such as antipsychotics or stimulants, depending on the condition of the patient. Most antidepressants will restrain the metabolism of serotonin and/or norepinephrine. Such drugs are called Selective Serotonin Reuptake Inhibitors (SSRI), and they actively attempt to prevent the aforementioned neurotransmitters from dropping to the levels at which depression is experienced. SSRIs will often take 3-5 weeks to have a noticeable effect, due to the inability of the brain to process the flood of serotonin and it reacts by downregulating the sensitivity of the autoreceptors, which can take up to 5 weeks. Currently, Bi-functional SSRIs are being researched, which will occupy the autoreceptors, bypassing the 'throttling' of serotonin. Another type of antidepressant is an Monoamine oxidase inhibitor, which are thought to block the actions of MAO, an enzyme which assists in the breakdown of serotonin and norepinephrine. MAOI's are typically only used in the event that a tricyclic antidepressant or SSRI fails to prevent or exacerbates depression.

Common Antidepressants:

- Fluoxetine (Prozac®), SSRI
- Bupropion HCl (Wellbutrin®), NDRI[2]
- Phenelzine (Nardil®), MAO Inhibitor
- Isocarboxazid (Marplan®), MAO Inhibitor

Mood stabilizers

Main article: Mood stabilizers

In 1949, the Australian John Cade discovered that lithium salts could control mania, reducing the frequency and severity of manic episodes. This introduced the now popular drug Lithium carbonate to the mainstream public, as well as being the first mood stabilizer to be approved by the Food & Drug Administration. Many antipsychotics are used as mood stabilizers, although typically the first resort would be a standard mood stabilizer such as Lithium carbonate. Many mood stabilizers, with the exception of Lithium, are anticonvulsants.

Common Mood Stabilizers:

- Lithium Carbonate (Carbolith®), Regular Mood stabilizer
- **Carbamazepine (Tegretol®),** Anticonvulsant Mood stabilizer
- **Valproic acid (Valproate),** Anticonvulsant Mood stabilizer
    - Valproate semisodium (Depakote®), Anticonvulsant Mood stabilizer

Stimulants

Main article: Stimulants

Stimulants are some of the most widely prescribed drugs today. A stimulant is any drug that stimulates the central nervous system. Adderall®, a collection of Amphetamine salts, is one of the most prescribed pharmaceuticals in the treatment of ADHD. Typically prescribed to treat adolescents with Attention Deficit Hyperactivity Disorder and though not FDA approved for Adults, it is very common as a treatment. Patients respond differently to each drug. Most frequently used are Timed-release mediums but if such a method doesn't work there are many options to try. Stimulants have the potential to be addictive and patients with a history of drug abuse are typically monitored closely or even barred from the usage and given an alternative. Discontinuing treatment without tapering the dosage is not advisable.

Common Stimulants[6]:

- Caffeine, Typical Stimulant found in many edibles worldwide
- Methylphenidate (Ritalin®), (Concerta®) atypical stimulant
- Dexmethylphenidate (Focalin®) D-isomer of Methylphenidate stimulant
- Dextroamphetamine (Dexedrine®), (Dextrostat®) D-Amphetamine-based stimulant
- Dextroamphetamine & Levoamphetamine (Adderall®), D,l-Amphetamine salt mix stimulant
- Methamphetamine {Desoxyn®), D-methamphetamine-based stimulant

Anxiolytics & Hypnotics

Barbiturates were first used as hypnotics and as anxiolytics, but as time went on, safer benzodiazepines (Lowell Randall and Leo Sternbach, 1957) were developed in the 1960s and 1970s. Eventually they led to billions of doses being consumed annually, but as prescriptions were increasing, even more was the abuse of them.

Common Anxiolytics & Hypnotics:

- Diazepam (Valium®), Benzodiazepine derivative
- Nitrazepam (Mogadon®), Benzodiazepine derivative
- Zolpidem (Ambien®, Stilnox®), an Imidazopyridine
- Chlordiazepoxide (Librium®), Benzodiazepine derivative

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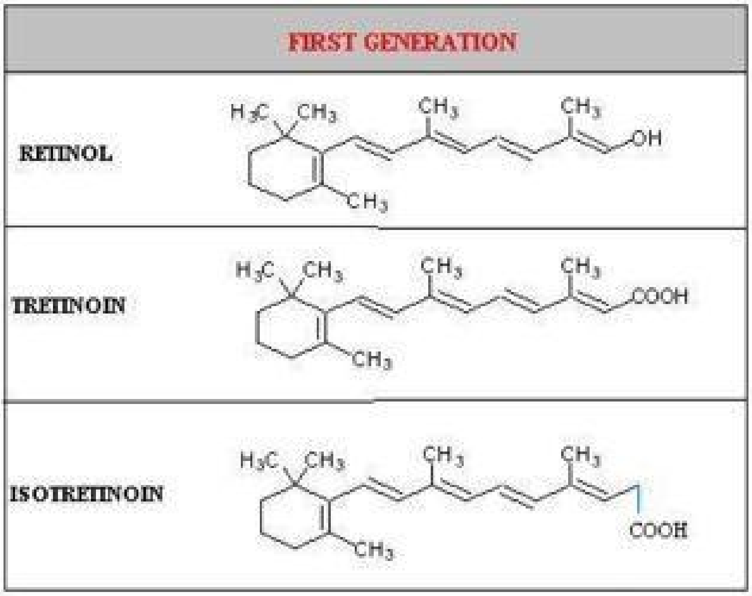
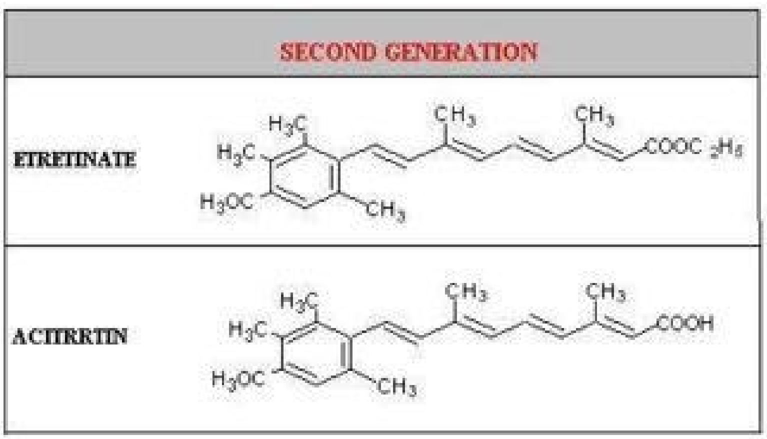
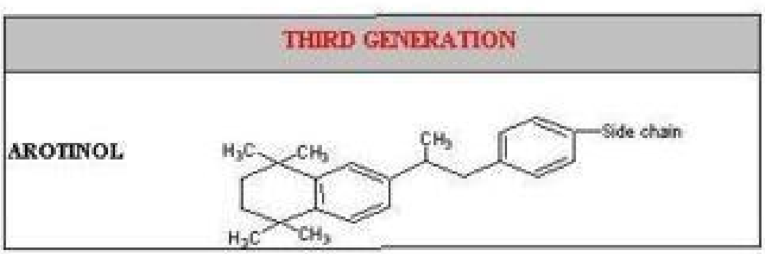
Retinoids







The *Retinoids* are a class of chemical compounds that are related chemically to vitamin A. Retinoids are used in medicine, primarily due to the way they regulate epithelial cell growth.

Retinoids have many important and diverse functions throughout the body including roles in vision, regulation of cell proliferation and differentiation, growth of bone tissue, immune function, and activation of tumor suppressor genes.

Research is also being done into their ability to treat skin cancers. Currently 9-cis retinoic acid may be used topically to help treat skin lesions from Kaposi's sarcoma.

Types

There are three generations of Retinoids:

- First generation retinoids: which include retinol, tretinoin (Retin-A), isotretinoin and alitretinoin.
- Second generation retinoids: which include etretinate and its metabolite acitretin.
- Third generation retinoids: which include tazarotene and bexarotene.

Structure

The basic structure of the retinoid molecule consist of a cyclic end group, a polyene side chain and a polar end group. The conjugated system formed by alternating C=C double bonds in the polyene side chain are responsible for the color of retinoids (typically yellow, orange, or red). Hence, many retinoids are chromophores. Alternation of side chains and end groups creates the various classes of retinoids.

First and Second generation retinoids are able to bind with several retinoid receptors due to the flexibility imparted by their alternating single and double bonds.

Third generation retinoids are less flexible than First and Second generation retinoids and therefore, interact with fewer retinoid receptors.

Uses

Retinoids are used in the treatment of many diverse diseases and are effective in the treatment of a number of dematological conditions such as inflammatory skin disorders, skin cancers, disorders of increased cell turnover(e.g. psoriasis), and photoaging.

Common skin conditions treated by retinoids include acne and psoriasis.

Toxicity

Toxic effects occur with prolonged high intake (in children 25,000-500,000 IU daily. A medical sign of chronic poisoning is the presence of painful tender swellings on the long bones. Anorexia, skin lesions, hair loss, hepatosplenomegaly, papilloedema, bleeding, general malaise, pseudotumor cerebri, and death may also occur.

Chronic overdose also causes an increased liability of biological membranes and of the outer layer of the skin to peel.

As vitamin A (retinoids) is stored in the liver, Eskimos never eat polar-bear liver, knowing it to be toxic, and husky dogs, with instinctive wisdom, also avoid it.

Recent research has suggested a role for retinoids in cutaneous adverse effects for a variety of drugs including the Antimalarial drug proguanil. It is proposed that drugs such as proguanil act to disrupt retinoid homeostasis.

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Retinol

Vitamin A (Retinol)

General

Chemical formula $C_{20}H_{30}O$

Molecular weight 286.456 g/mol

Vitamin properties

Solubility Fat

RDA (adult male) 900 µg/day

RDA (adult female) 700 µg/day

RDA upper limit (adult male) 3,000 µg/day

RDA upper limit (adult female) 3,000 µg/day

Deficiency symptoms

- Night blindness
- Keratomalacia
- Pale, dry skin

Excess symptoms

- Liver toxicity
- Dry skin
- Hair loss

- Teratological **effects**
    - Osteoporosis (suspected, long-term)

Common sources

- Liver
- Dairy products
- Darkly colored fruits
- Leafy vegetables

Retinol, the animal form of vitamin A, is a yellow fat-soluble, antioxidant vitamin important in vision and bone growth. It belongs to the family of chemical compounds known as retinoids. Retinol is ingested in a precursor form; animal sources (milk and eggs) contain retinyl esters, whereas plants (carrots, spinach) contain pro-vitamin A carotenoids. Hydrolysis of retinyl esters results in retinol while pro-vitamin A carotenoids can be cleaved to produce retinal. Retinal, also known as retinaldehyde, can be reversibly reduced to produce retinol or it can be irreversibly oxidized to produce retinoic acid. The best described active retinoid metabolites are 11-cis-retinal and the all-trans and 9-cis-isomers of retinoic acid.

Discovery

In 1913, Elmer McCollum, a biochemist at the University of Wisconsin-Madison, and colleague Marguerite Davis identified a fat-soluble nutrient in butterfat and cod liver oil. Their work confirmed that of Thomas Osborne and Lafayette Mendel, at Yale, which suggested a fat-soluble nutrient in butterfat, also in 1913 [1]. Vitamin A was first synthesized in 1947.

Chemical structure and function

Many different geometric isomers of retinol, retinal and retinoic acid are possible as a result of either a trans or cis configuration of the four double bonds found in the polyene chain. The cis isomers are less stable and can readily convert to the all-trans configuration (as seen in the structure of all-trans-retinol shown here). Nevertheless, some cis isomers are found naturally and carry out essential functions. For example, the 11-cis-retinal isomer is the chromophore of rhodopsin, the vertebrate photoreceptor molecule. Rhodopsin is comprised of the 11-cis-retinal covalently linked via a Schiff base to the opsin protein (either rod opsin or blue, red or green cone opsins). The process of vision relies on the light-induced isomerisation of the chromophore from 11-cis to all-trans resulting in a change of the conformation and activation of the photoreceptor molecule. One of the earliest signs of vitamin A deficiency is night-blindness followed by decreased visual acuity.

George Wald won the 1967 Nobel Prize in Physiology or Medicine for his work with retina pigments (also called visual pigments), which led to the understanding of the role of vitamin A in vision.

Many of the non-visual functions of vitamin A are mediated by retinoic acid, which regulates gene expression by activating intracellular retinoic acid receptors. The non-visual functions of vitamin A are essential in the immunological function, reproduction and embryonic development of vertebrates as evidenced by the impaired growth, susceptibility to infection and birth defects observed in populations receiving suboptimal vitamin A in their diet.

Retinol can also be used in the treatment of acne in a topical cream. A form of retinoic acid, all-trans retinoic acid (ATRA) is currently used as chemotherapy for acute promyelocytic leukemia, a subtype of acute myelogenous leukemia. This is because cells of this subtype of leukemia are sensitive to agonists of the retinoic acid receptors (RARs).

Vision

Vitamin A is required in the production of rhodopsin, the visual pigment used in low light levels. This is why eating foods rich in vitamin A is said to allow you to see in the dark.

Epithelial Cells

Vitamin A is essential for the correct functioning of epithelial cells. In Vitamin A deficiency, mucus-secreting cells are replaced by keratin producing cells, leading to xerosis.

Glycoprotein synthesis

Glycoprotein synthesis requires adequate Vitamin A status. In severe Vitamin A deficiency, lack of glycoproteins may lead to corneal ulcers or liquefaction.

Immune System

Vitamin A is essential to maintain intact epithelial tissues as a physical barrier to infection; it is also involved in maintaining a number of immune cell types from both the innate and acquired immune systems. These include the lymphocytes (B-cells, T-cells, and natural killer cells), as well as many myelocytes (neutrophils, macrophages, and myeloid dendritic cells).

Formation of red blood cells (Haematopoiesis)

Vitamin A may be needed for normal haematopoiesis; deficiency causes abnormalities in iron metabolism.

Growth

Vitamin A affects the production of human growth hormone.

Units of measurement

When referring to dietary allowances or nutritional science, retinol is usually measured in international units (IU). IU refers to biological activity and therefore is unique to each individual compound, however 1 IU of retinol is equivalent to approximately 0.3 micrograms (300 nanograms).

Nutrition

This vitamin plays an essential role in vision, particularly night vision, normal bone and tooth development, reproduction, and the health of skin and mucous membranes (the mucus-secreting layer that lines body regions such as the respiratory tract). Vitamin A also acts in the body as an antioxidant, a protective chemical that may reduce the risk of certain cancers.

There are two sources of dietary vitamin A. Active forms, which are immediately available to the body are obtained from animal products. These are known as retinoids and include retinal and retinol. Precursors, also known as provitamins, which must be converted to active forms by the body, are obtained from fruits and vegetables containing yellow, orange and dark green pigments, known as carotenoids, the most well-known being beta-carotene. For this reason, amounts of vitamin A are measured in Retinal Equivalents (RE). One RE is equivalent to 0.001mg of retinal, or 0.006mg of beta-carotene, or 3.3 International Units of vitamin A.

In the intestine, vitamin A is protected from being chemically changed by vitamin E. Vitamin A is fat-soluble and can be stored in the body. Most of the vitamin A you eat is stored in the liver. When required by a particular part of the body, the liver releases some vitamin A, which is carried by the blood and delivered to the target cells and tissues.

Dietary intake

The Dietary Reference Intake (DRI) Recommended Daily Amount (RDA) for Vitamin A for a 25-year old male is 900 micrograms/day, or 3,000 IU.

During the absorption process in the intestines, retinol is incorporated into chylomicrons as the ester form, and it is these particles that mediate transport to the liver. Liver cells (hepatocytes) store vitamin A as the ester, and when retinol is needed in other tissues, it is de-esterifed and released into the blood as the alcohol. Retinol then attaches to a serum carrier, retinol binding protein, for transport to target tissues. A binding protein inside cells, cellular retinoic acid binding protein, serves to store and move retinoic acid intracellularly. Carotenoid bioavailability ranges between 1/5 to 1/10 of retinol's. Carotenoids are better absorbed when ingested as part of a fatty meal. Also, the carotenoids in vegetables, especially those with tough cell walls (e.g. carrots), are better absorbed when these cell walls are broken up by cooking or mincing.

Topical use

All retinoid forms of vitamin A are used in cosmetic and medical applications applied to the skin.

Retinoic acid, retinyl palmitate, isotretinoin, tretinoin and retinol are all used medicinally as a topical treatment for acne and keratosis pilaris. Isotretinoin is also used orally (under the trade names Accutane and Roaccutane), generally for severe or recalcitrant acne.

In cosmetics, vitamin A derivatives are used as so-called antiaging chemicals- vitamin A is absorbed through the skin and increases the rate of skin turnover, and gives a temporary increase in collagen giving a more youthful appearance.

Vitamin A deficiency

Vitamin A deficiency is common in developing countries but rarely seen in developed countries. Approximately 250,000 to 500,000 malnourished children in the developing world go blind each year from a deficiency of vitamin A. Night blindness is one of the first signs of vitamin A deficiency. Vitamin A deficiency contributes to blindness by making the cornea very dry and damaging the retina and cornea.

Vitamin A deficiency also diminishes the ability to fight infections. In countries where children are not immunized, infectious disease like measles have relatively higher fatality rates. As elucidated by Dr. Alfred Sommer, even mild, subclinical deficiency can also be a problem, as it may increase children's risk of developing respiratory and diarrheal infections, decrease growth rate, slow bone development, and decrease likelihood of survival from serious illness.

In addition to dietary problems, there are other causes of vitamin A deficiency. Iron deficiency can affect vitamin A uptake. Excess alcohol consumption can deplete vitamin A, and a stressed liver may be more susceptible to vitamin A toxicity. People who consume large amounts of alcohol should seek medical advice before taking vitamin A supplements.

Treatment of vitamin A deficiency can be undertaken with both oral and injectable forms, generally as vitamin A palmitate.

Vitamin A overdose (Toxicity)

The Tolerable Upper Intake Level (UL) for vitamin A, for a 25-year old male, is 3,000 micrograms/day, or about 10,000 IU.

Too much vitamin A can be harmful or fatal, resulting in what is known as hypervitaminosis A. The body converts the dimerized form, carotene, into vitamin A as it is needed, therefore high levels of carotene are not toxic compared to the ester (animal) forms. The livers of certain animals, especially those adapted to polar environments, often contain amounts of vitamin A that would be toxic to humans. Thus, vitamin A toxicity is typically reported in arctic explorers and people taking large doses of synthetic vitamin A. The first documented death due to vitamin A poisoning was Xavier Mertz, a Swiss scientist who died in January 1913 on an Antarctic expedition that had lost its food supplies and fell to eating its sled dogs. Mertz consumed lethal amounts of vitamin A by eating the dogs' livers. Just 0.3

grams of the liver of the polar bear contains the upper intake level.[2] If eaten in one meal, 30 to 90 grams is enough to kill a human being, or to make even sled dogs very ill.

Excess vitamin A has also been suspected to be a contributor to osteoporosis. This seems to happen at much lower doses than those required to induce acute intoxication. Only preformed vitamin A can cause these problems, because the conversion of carotenoids into vitamin A is downregulated when physiological requirements are met. An excessive uptake of carotenoids can, however, cause carotenosis.

The carotenoid beta carotene was interestingly associated with an increase in lung cancer when it was studied in a lung cancer prevention trial in male smokers. In non-smokers, the opposite effect has been noted.

Excess preformed vitamin A during early pregnancy has also been associated with a significant increase in birth defects. These defects may be severe, even life-threatening. Even twice the daily recommended amount can cause severe birth defects.The FDA currently recommends that pregnant women get their Vitamin A from foods containing beta carotene and that they should ensure that they consume no more than 5,000 IU of preformed Vitamin A (if any) per day. Although Vitamin A is necessary for fetal development, most women carry stores of Vitamin A in their fat cells, so oversupplementation should be strictly avoided.

Good sources

Vitamin A is found naturally in many foods. Each of the following contains at least 0.15mg of Vitamin A or beta carotene per 1.75-7 oz. (50-200g):

- Sweet potatoes

Carrots
Collard greens
Kale
Pumpkin
Spinach
Sweet peppers
Winter squash
Apricots
Cantaloupe melon
Mango
Liver (polar bear, beef, pork, chicken, or turkey)
Eggs
Broccoli

Night vision

Night blindness - the inability to see well in dim light - is associated with a deficiency of vitamin A. This vitamin is needed for the formation of rhodopsin. This is a pigment located in the eye's retina, which is the light-sensitive tissue lining in the back of the eye.

When stimulated by light, rhodopsin splits into two proteins: opsin and retinal (a form of vitamin A); when it is dark the reverse reaction occurs - the retinal and opsin combine to re-form rhodopsin, a reaction that requires extra retinal.

Without adequate amounts of retinal, regeneration of rhodopsin is incomplete and night blindness occurs. Since carrots are a good source of beta-carotene, there is truth in the old belief that carrots help you see better in the dark.

Closely related chemicals

- Isotretinoin (Tradename: Accutane(US), Roaccutane)

Retinyl palmitate ('vitamin A' aka. "pro-vitamin A")
All-trans retinoic acid

Genetically engineered vitamin A enriched rice

Due to the high prevalence of vitamin A deficiency in developing countries, there are efforts to produce genetically modified rice rich in beta carotene. The idea is that this would help poor people, who can't afford a varied diet containing sufficient natural sources of vitamin A, meet their dietary needs. The golden rice project is one such effort, and is already undergoing trials.

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Teratogens

Teratogenesis is a medical term from the Greek, literally meaning monster-making, which derives from teratology, the study of the frequency, causation, and development of congenital malformations—misleadingly called birth defects. These include gross morphological abnormalities, such as cleft lip and/or palate, anencephaly, or ventricular septal defect, but may also include phenomena such as increased risk of cervical cancer or discoloration of tooth enamel. These malformations can arise from genetic abnormalities of the fetus, from adverse environmental circumstances (termed *teratogens* or *tetragens*), or a combination of these factors. Teratogenesis has gained a more specific usage for the development of abnormal cell masses during fetal growth (see pregnancy), causing physical defects in the fetus. The study of teratogenesis is called teratology.

Known teratogens

The American College of Occupational and Environmental Medicine recognizes the following teratogens.

- Ionizing radiation: atomic weapons, radioiodine, radiation therapy
- Infections: cytomegalovirus, herpes virus hominis I and II, parvovirus B-19, rubella virus (German measles), syphilis, toxoplasmosis, Venezuelan equine encephalitis virus
- Metabolic imbalance: alcoholism, endemic cretinism, diabetes, folic acid deficiency, hyperthermia, phenylketonuria, rheumatic disease and congenital heart block, virilizing tumors
- Drugs and environmental chemicals: 13-cis-retinoic acid (isotretinoin, Accutane), aminopterin and methylaminopterin, androgenic hormones, busulfan, captopril and enalapril (ACE inhibitors), chlorobiphenyls (PCBs), cocaine, coumarin anticoagulants, cyclophosphamide, diethylstilbestrol, diphenylhydantoin (Phenytoin, Dilantin, Epanutin), etretinate, lithium, methimazole, organic mercury compounds, penicillamine, tetracyclines, thalidomide, trimethadione, and valproic acid.

The status of some of the above substances (e.g. diphenylhydantoin) is subject to debate, and many other compounds are under varying degrees of suspicion. These include Agent Orange[1], nicotine[2], aspirin and other NSAIDs, and birth control pills. Other compounds are known as severe teratogens based on veterinary work and animal studies, but aren't listed above because they have not been studied in humans, e.g. cyclopamine. Teratogenic effects also help to determine the pregnancy category assigned by regulatory authorities; in the United States, a pregnancy category of X, D, or C may be assigned if teratogenic effects (or other risks in pregnancy) are documented or cannot be excluded.

Isotretinoin (13-cis-retinoic-acid; brand name Accutane), often used to treat severe acne, is such a strong teratogen that just a single dose taken by a pregnant woman may result in serious birth defects. Because of this effect, most countries have systems in place to ensure that it is not given to pregnant women, and that the patient is aware of how important it is to prevent pregnancy during and at least one month after treatment. Medical guidelines also

suggest that pregnant women should limit vitamin A intake to about 700 ¼g/day, as it has teratogenic potential when consumed in excess.[3][4]

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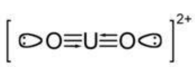
Uranyl compounds


The uranyl ion, showing the U-O bond order of 3

The *uranyl* ion is the dipositive cation UO_2^{2+}, which forms salts with acids. In this ion, uranium is in its +6 oxidation state. The other common oxidation state of uranium is uranium(IV), called uranous. The uranyl ion is the most common species encountered in the aqueous chemistry of uranium. Solid uranyl compounds are often colored red, yellow, orange or green. Like all uranium compounds, uranyl compounds are toxic. The toxicity of soluble uranyl salts is higher due to their faster incorporation into tissues.

Examples

Examples of uranyl compounds include:

- Uranium trioxide, UO_3
- Uranyl acetate, $UO_2(C_2H_3O_2)_2$
- Uranyl ammonium carbonate, $UO_2CO_3 \cdot 2(NH_4)_2CO_3$
- Uranyl carbonate, UO_2CO_3
- Uranyl chloride, UO_2Cl_2
- Uranyl hydroxide, $UO_2(OH)_2$ or $(UO_2)_2(OH)_2$ also in aqueous

- Uranyl nitrate, $UO_2(NO_3)_2$
- Uranyl sulfate, UO_2SO_4
- Uranyl zinc acetate, $ZnUO_2(CH_3COO)_4$

Minerals

Such minerals occur in oxidised portions of uranium ore deposits. Common uranyl minerals include tyuyamunite (Ca(UO2)2V2O8·8H2O), autunite (Ca(UO2)2(PO4)2·8-12H2O), torbernite (Cu(UO2)2 (PO4)·8-12H2O) and uranophane ($(H_3O)_2$Ca $(UO_2)_2(SiO_4)\cdot 3H_2O$) (Hutchinson and Blackwell, 1984). Uranyl minerals, which contain uranium(VI) can help show the genesis of uranium deposits and the water-rock interactions that occur in uranium-rich mineral seams.

Chemistry

Uranium chemistry has traditionally revolved around the aqueous chemistry of the uranyl ion, and related molecular species. One important use of this chemistry is for preparation of uranium dioxide ceramic pellets that are used as the fuel in light water nuclear reactors. Often the fuel materials start to break down chemically before the uranium is completely spent, and this too is an active area of investigation, as many of the corrosion products are of the uranyl group.

Structure

The geometry of the uranyl ion has been the subject of much debate. The close approach of two oxygen atoms to uranium, with each linear O-U-O bond from 1.7 to 1.9 Å, prevents the close approach of a third or more. d-p and f-p bonding have been suggested to explain the short U-O bonds.[1]

Health and environmental issues

Uranyl nitrate is an oxidizing and highly toxic compound and should not be ingested; it causes severe renal insufficiency and acute tubular necrosis and is a lymphocyte mitogen.

Target organs include the kidneys, liver, lungs and brain. Uranyl ion accumulation in tissues including gonocytes[2] produces congenital disorders, and in white blood cells causes immune system damage.[3] Uranyl compounds are also neurotoxins.

Combustion of uranium

Aerial oxidation of any uranium compound eventually results in the formation of a uranyl compound.[1] Uranyl ion contamination has been found on and around depleted uranium targets.[4]

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Agent Orange

Agent Orange was the nickname given to a powerful herbicide and defoliant used by the U.S. military in its Herbicidal Warfare program during the Vietnam War. Agent Orange was used from 1961 to 1971, and was by far the most used of the so-called "rainbow herbicides" used during the program. Agent Orange (as well as Agents Purple, Pink, Blue, White, and Green) contained dioxins which are known to have caused harm to the health of those exposed during the Vietnam War. Studies of populations highly exposed to dioxin indicate increased risk of various types of cancer and genetic defects; the effect of long term low level exposure has not been established. Since the 1980s, several lawsuits have been filed against the companies who produced Agent Orange, among them being Dow Chemical and Monsanto. U.S. veterans obtained $180 million in compensation in 1984, while Australian, Canadian and New Zealand veterans also obtained compensation in an out-of-court settlement the same year. In 1999, 20,000 South Koreans filed a lawsuit in Korea; in January 2006, the Korean Appeal Court ordered Monsanto and Dow to pay $62 million in compensation to about 6,800 people. However, no Vietnamese have obtained compensation, and on March 10, 2005 Judge Jack Weinstein of Brooklyn Federal Court dismissed the lawsuit filed by the Vietnamese victims of Agent Orange against the chemical companies that produced the defoliants/herbicides.

Description

Agent Orange is a roughly 1:1 mixture of two phenoxy herbicides in ester form, 2,4-dichlorophenoxyacetic acid (2,4-D) and 2,4,5-trichlorophenoxyacetic acid (2,4,5-T). These herbicides were developed during the 1940s by independent teams in England and the United States for use in controlling broad-leaf plants. Phenoxy agents work by mimicking a plant growth hormone, indoleacetic acid (IAA). When sprayed on broad-leaf plants they induce rapid, uncontrolled growth, eventually killing them. When sprayed on crops such as wheat or corn, it selectively kills just the broad-leaf plants in the field - the weeds - leaving

the crop relatively unaffected. First introduced in 1946, these herbicides were in widespread use in agriculture by the middle of the 1950s.

It was later learned that a dioxin, 2,3,7,8-tetrachlorodibenzo-para-dioxin (TCDD), is produced as a byproduct of the manufacture of 2,4,5-T, and was thus present in any of the herbicides that used it. The *National Toxicology Program* has classified TCDD to be a human carcinogen, frequently associated with soft-tissue sarcoma, Non-Hodgkin's lymphoma, Hodgkin's disease and chronic lymphocytic leukemia (CLL). 2,4,5-T has since been banned for use in the US and many other countries.

The herbicide 2,4-D does not contain dioxin, and it remains one of the most-used herbicides in the world today.

Diseases associated with dioxin exposure are chloracne, soft tissue sarcomas, Hodgkin's lymphoma, and non-Hodgkin's lymphoma. A link has also been found to diabetes, in a study by the Institute of Medicine[1]. Diseases with limited evidence of an association with Agent Orange are respiratory cancers, prostate cancer, multiple myeloma, Porphyria cutanea tarda (a type of skin disease), acute and subacute transient peripheral neuropathy, spina bifida, Type 2 diabetes, and acute myelogenous leukemia found only in the second or third generation. Diseases with inadequate or insufficient evidence of an association are hepatobiliary cancers, nasal or nasophargyngeal cancers, bone cancer, female reproductive cancers, renal cancer, testicular cancer, leukemia, spontaneous abortion, birth defects, neonatal or infant death and stillbirths, low birth weight, childhood cancers, abnormal sperm parameters, cognitive neuropsychiatric disorders, ataxia, peripheral nervous system disorders, circulatory disorders, respiratory disorders, skin cancers, urinary and bladder cancer. Diseases with limited or suggestive evidence of no association are gastrointestinal tumors such as stomach cancer, pancreatic cancer, colon cancer, and rectal cancer, and brain tumors.

Use in South East Asia (1961-1971)

This section covers the use of all of the "rainbow" herbicides.

During the Vietnam War, the US instituted a massive herbicidal program that ran from 1961 through 1971. The aim of the program was two-fold, one to destroy the "cover" provided by the jungle-like forest, and another to deny food to the enemy. First named Operation Trail Dust, then Operation Hades, it was finally renamed Operation Ranch Hand.

A variety of chemicals were tested or used operationally during this program. The primary broad-leaf herbicides sprayed during the "testing" phase of the program between 1962 and 1964 were Agent Orange, Agent Purple and Agent White. The chemicals themselves had no color; the names refer to colored stripes painted on the 55 gallon barrels to identify their contents. Much smaller amounts of other herbicides were also tested, including Agent Pink, Agent Green, Dinoxol, Trinoxol, Bromacil, Diquat, Tandex, Monuron, Diuron and Dalapon. Agent Blue was an unrelated herbicide based primarily on arsenic used to kill rice plants which were not susceptible to the phenoxy-based agents. A variety of Paraquat-related chemicals were apparently also tested in this role. For spraying, the various agents were mixed with kerosene or diesel fuel.

By 1964 the testing phase had ended, and Agent Orange was selected as the most effective agent for "territory denial". Operational use started in January 1965, increasing in breadth as logistical problems were solved. Most of Agent Orange sprayed during the program was delivered from modified US Air Force C-123K Provider aircraft under a program known as Operation Ranch Hand. Other delivery methods included helicopters, truck and hand spraying, notably for the areas directly around US bases. From 1968 on, an improved version known as "Orange II" or "Super Orange" was used as well.

Spraying reached its maximum during the most intense period of the war, between 1967 and 1968. After that the program "drew down", and ended in 1971. By this point an estimated 19 million gallons of herbicide had been sprayed on Vietnam, Cambodia, Thailand and Laos, somewhat more than half (55%) of that Agent Orange, between 1962 and 1971. Early estimates from 1974 had placed the amounts lower, between 12 and 14 million US gallons (45,000 and 53,000 m^3). In total about 6 million acres (24,000 km^2) were sprayed in Vietnam alone.

Effects of the program

The New Jersey Agent Orange Commission

In 1980, New Jersey created the New Jersey Agent Orange Commission, the first state commission created to study its effects. The Commission's research project in association with Rutgers University was called "The Pointman Project". It was disbanded by governor Christine Todd Whitman in 1996.

During Pointman I, Commission researchers devised ways to determine small dioxin levels in blood. Prior to this, such levels could only be found in the adipose (fat) tissue. The project compared dioxin levels in a small group of Vietnam veterans who had been exposed to Agent Orange with a group of matched veterans who had not served in Vietnam. The results of this project were published in the Journal of the American Medical Association (JAMA) in 1988.(Vol. 259 No. 11, March 18, 1988).

The second phase of the project continued to examine and compare dioxin levels in various groups of Vietnam veterans including Army, Marines and brown water riverboat Navy personnel. In addition, the Commission was the only agency to examine such levels in women who served in Vietnam.

The National Academy of Science 2003 report

An April 2003 report paid for by the National Academy of Sciences concluded that during the Vietnam War, 3,181 villages were sprayed directly with herbicides. Between 2.1 and 4.8 million people "would have been present during the spraying." Furthermore, many US citizens were given access to military records and Air Force operational folders previously not studied. The re-estimate made by the report places the volume of herbicides sprayed between 1962 and 1971 to a level 7,131,907 liters more than an uncorrected estimate published in 1974 and 9.4 million more liters than a 1974 corrected inventory. It was

produced under contract for the Army by Diamond Shamrock, Dow, Hercules, Monsanto, T-H Agricultural & Nutrition, Thompson Chemicals, and Uniroyal.

The National Academy of Sciences undertook a survey of the scientific literature on the health effects of dioxin exposure, listing a number of health effects associated with significant exposure. The study is updated every two years.

The independent Institute of Medicine announced in 2006 that there appear to be no clear links to Agent Orange and cancer. They did appear to confirm a link to diabetes.

New Zealand direct involvement

In 2005, the New Zealand government confirmed that it supplied Agent Orange chemicals to the United States military during the conflict. Since the early 1960s, and up until 1987, it manufactured the 2,4,5T herbicide at a plant in New Plymouth which was then shipped to U.S. military bases in South East Asia.

Lawsuits

In 1984, Agent Orange manufacturers paid Australian, Canadian and New Zealand veterans in an out-of-court settlement [1].

US Vietnamese victims class action lawsuit

On January 31, 2004, a victim's rights group, the Vietnam Association for Victims of Agent Orange/Dioxin (VAVA), filed a lawsuit in a US Federal District Court in Brooklyn, New York, against several US companies, for liability in causing personal injury, by developing and producing the chemical. Dow Chemical and Monsanto were the two largest producers of Agent Orange for the US military, and were named in the suit along with the dozens of other companies (Diamond Shamrock, Uniroyal, Thompson Chemicals, Hercules, etc.). A number of lawsuits by American GIs were settled out of court - without admission of guilt by the chemical companies - in the years since the Vietnam War. In 1984, chemical companies that manufactured Agent Orange paid $180 million into a fund for United States veterans following a lawsuit.

On March 10, 2005, the District Court judge Jack Weinstein - who had defended the US veterans victims of Agent Orange - dismissed the suit, ruling that there was no legal basis for the plaintiffs' claims. The judge concluded that Agent Orange was not considered a poison under international law at the time of its use by the US; that the US was not prohibited from using it as an herbicide; and that the companies which produced the substance were not liable for the method of its use by the government. The US government is not a party in the lawsuit, claiming sovereign immunity.

On September 30, 2005, the Vietnamese victims lodged an appeal in the Second Circuit Court of Appeals; it is expected that the Court of Appeals will hold an oral argument sometime in Fall 2006. At this point the appeal is focused on whether or not the case will be reinstated and go to trial.

In order to assist those who have been impacted by Agent Orange/Dioxin, the Vietnamese have established "Peace villages", which each host between 50 to 100 victims, giving them medical and psychological help. As of 2006, there were 11 such Peace villages, thus granting some social protection to fewer than a thousand victims. US veterans of the war in Vietnam, NGOs and individuals who are aware and sympathetic to the impacts of Agent Orange have also supported these programs in Vietnam. An international group of Veterans from the US and its allies during the Vietnam war working together with their former enemy - veterans from the Vietnam Veterans Association - established the Vietnam Friendship Village[7] located outside of Hanoi. The center provides medical care, rehabilitation and vocational training for children and veterans from Vietnam who have been impacted by Agent Orange.

The US Veterans Administration has listed prostate cancer, respiratory cancers, multiple myeloma, type II diabetes, Hodgkin's disease, non-Hodgkin's lymphoma, soft tissue sarcoma, chloracne, porphyria cutanea tarda, peripheral neuropathy, and spina bifida in children of veterans exposed to Agent Orange as side effects of the herbicide.

South Korean lawsuit

In 1999, about 20,000 South Koreans filed two separated lawsuits against US companies, seeking more than $5 billion in damages. After losing a decision in 2002, they filed an appeal. In January 2006, the South Korean Appeals Court ordered Dow Chemical and Monsanto to pay $62 million in compensation to about 6,800 people. The ruling acknowledged that "the defendants failed to ensure safety as the defoliants manufactured by the defendants had higher levels of dioxins than standard", and, quoting the U.S. National Academy of Science report, declared that there was a "causal relationship" between Agent Orange and 11 diseases, including cancers of the lung, larynx and prostate. However, the judges failed to acknowledge "the relationship between the chemical and peripheral neuropathy, the disease most widespread among Agent Orange victims" according to the Mercury News. South Koreans were the largest foreign contingent of US allies in Vietnam, contributing some 320,000 troops. They lost 5,077 soldiers and suffered 10,962 wounded, according to the Mercury News[1].

Miscellaneous

- The Union Carbide company produced the constituents of Agent Orange at Homebush Bay in Sydney, Australia where the 2000 Summer Olympics were staged.
- The Uniroyal plant in Elmira, Ontario was one of seven suppliers producing Agent Orange for the U.S. military's use in Vietnam.
- An international committee[2] in support of Vietnamese victims of Agent Orange, has published a report on the impact of Agent Orange in Vietnam.[3][4]

Cultural references

Due to its politically sensitive nature, Agent Orange has become a common topic for reference in popular culture.

- For example: the songs "Orange Crush" by R.E.M, Anti-Flag's "Die for your Government" and "Depleted Uranium is a War Crime", Rage Against the Machine's "Sleep Now In The Fire", Oysterhead's "Shadow of a Man"; the album Agent Orange from German thrash metal band Sodom; the song "Agent Orange" by Depeche Mode; the punk band Agent Orange. A Filipino band named Slapshock also wrote a song entitled "Agent Orange," though the lyrics have no connection to the herbicide. An American rap artist named "Cage" wrote a song entitled "Agent Orange" that sampled the theme music from Stanley Kubrick's "A Clockwork Orange", but contains no reference to the herbicide.
- On her "Boys for Pele" album, Tori Amos has an instrumental song entitled "Agent Orange".
- The song "Uncommon Valor: A Vietnam Story" by Jedi Mind Tricks, contains the lyrics: "I escaped the war, came back/ But ain't escape Agent Orange, two of my kids born handicapped/ Spastic, quadriplegic, micro cephalic/ Cerebral palsy, cortical blindness, name it they had it"
- In a Season One episode of The X-Files entitled 'E.B.E', a group known as the Lone Gunmen refer to shells coated in depleted uranium as 'the Agent Orange of the 90s'.
- A South African blues musician goes by the name of Simon 'Agent' Orange.*In his stand-up routine, the British comedian Jack Dee has referred to an estate agent wearing excessive amounts of aftershave lotion as "Estate Agent Orange" because of the irritating effect on his eyes. In the video game Grand Theft Auto: Vice City a parody commercial is made advertising a product called "Agent Orange".

Further reading

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See also

- Depleted uranium
- Thalidomide

Depleted uranium

Depleted uranium (DU) is uranium that has a reduced proportion of the isotope Uranium-235. It is mostly made up of Uranium-238. The names *Q-metal*, *depletalloy*, and *D-38*, which once applied to depleted uranium, have fallen into disuse.

Its high strength and density have made it a valued component in some technical applications, specifically in military projectiles. Such uses remain controversial, as U-238 is still radioactive.

Sources

Depleted uranium is a byproduct of the enriching of natural uranium for use in nuclear reactors. When most of the fissile radioactive isotopes of uranium are removed from natural uranium, the residue is called depleted uranium. A less common source of the material is reprocessed spent reactor fuel. The origin can be distinguished by the content of uranium-236,[1] produced by neutron capture from uranium-235 in nuclear reactors.

As a toxic and radioactive waste product that requires long term storage as low level nuclear waste, depleted uranium is costly to keep but relatively inexpensive to obtain. Generally the only real costs are those associated with conversion of UF6 to metal. It is extremely dense, 67% denser than lead, only slightly less than tungsten and gold, and just 16% less dense than osmium or iridium, the densest naturally occurring substances known. Its low cost makes it attractive for a variety of uses. However, the material is prone to corrosion and small particles are pyrophoric.

History

Depleted uranium was first stored in stockpiles in the 1940s when the U.S. and USSR began their nuclear weapons and nuclear power programs. While it is possible to design civilian power reactors with unenriched fuel, only about 10% of reactors ever built utilize that technology, and both nuclear weapons production and naval reactors require the concentrated isotope. Originally, DU was conserved in the hope that more efficient enrichment techniques would allow further extraction of the fissile isotope; however, those hopes have not materialized.

In the 1970s, The Pentagon reported that the Soviet military had developed armor plating for Warsaw Pact tanks that NATO ammunition couldn't penetrate. The Pentagon began searching for material to make denser bullets. After testing various metals, ordnance researchers settled on depleted uranium. DU was useful in ammunition not only because of its unique physical properties and effectiveness, but also because it was cheap and readily available. Tungsten, the only other candidate, had to be sourced from China. With DU stockpiles estimated to be more than 500,000 tons, the financial burden of housing this amount of low-level radioactive waste was very apparent. It was therefore more economical to use depleted uranium rather than storing it. Thus, from the late 1970s, the U.S., the Soviet Union, Britain and France, began converting their stockpiles of depleted uranium into kinetic energy penetrators.

Photographic evidence of destroyed equipment suggests that DU was first used during the 1973 Arab-Israeli war. Various written reports cite information that was obtained as a consequence of that use.[1]

However, while clearing the decades-old Hawaii Stryker firing range, workers have found chemical weapons from World War I era and depleted uranium ammunition from the 1960s

Production and availability

Natural uranium metal contains about 0.71% U-235, 99.28% U-238, and about 0.0054% U-234. In order to produce enriched uranium, the process of isotope separation removes a substantial portion of the U-235 for use in nuclear power, weapons, or other uses. The remainder, depleted uranium, contains only 0.2% to 0.4% U-235. Because natural uranium begins with such a low percentage of U-235, the enrichment process produces large quantities of depleted uranium. For example, producing 1 kg of 5% enriched uranium requires 11.8 kg of natural uranium, and leaves about 10.8 kg of depleted uranium with only 0.3% U-235 remaining.

The Nuclear Regulatory Commission (NRC) defines depleted uranium as uranium with a percentage of the **235**U isotope that is less than 0.711% by weight (See 10 CFR 40.4.) The military specifications designate that the DU used by DoD contain less than 0.3% **235**U (AEPI, 1995). In actuality, DoD uses only DU that contains approximately 0.2% **235**U (AEPI, 1995).

World Depleted Uranium Inventory

Country	Organization	DU Stocks (in tonnes)	Reported
USA	DOE	480,000	2002
Russia	FAEA	460,000	1996
France	COGEMA	190,000	2001
Israel	BNFL	50,000	2001
UK	BNFL	30,000	2001
Germany	URENCO	16,000	1999
Japan	JNFL	10,000	2001
China	CNNC	2,000	2000
South Korea	KAERI	200	2002
South Africa	NECSA	73	2001
TOTAL		**1,188,273**	**2002**

Source: WISE Uranium Project

Military applications

Depleted uranium is very dense; at 19050 kg/m^3, it is 70% denser than lead. Thus a given weight of it has a smaller diameter than an equivalent lead projectile, with less aerodynamic drag and deeper penetration due to a higher pressure at point of impact. DU projectile ordnance is often incendiary because of its pyrophoric property.

Armor plate

Because of its high density, depleted uranium can also be used in tank armor, sandwiched between sheets of steel armor plate. For instance, some late-production M1A1HA and M1A2 Abrams tanks built after 1998 have DU reinforcement as part of its armor plating in the front of the hull and the front of the turret and there is a program to upgrade the rest.

Ammunition

Most military use of depleted uranium has been as 30 mm and smaller ordnance, primarily the 30 mm PGU-14/B armour-piercing incendiary round from the GAU-8 Avenger cannon of the A-10 Thunderbolt II [4] used by the U.S. Air Force. 25 mm DU rounds have been used in the M242 gun mounted on the U.S. Army's Bradley Fighting Vehicle and LAV-AT. The U.S. Marine Corps uses DU in the 25 mm PGU-20 round fired by the GAU-12 Equalizer cannon of the AV-8B Harrier, and also in the 20 mm M197 gun mounted on AH-1 helicopter

gunships. The US Navy's Phalanx CIWS's M61 Vulcan gatling gun used 20 mm armor-piercing penetrator rounds with discarding plastic sabots which were made using depleted uranium, later changed to tungsten.

Another use of depleted uranium is in kinetic energy penetrators anti-armor role. Kinetic energy penetrator rounds consist of a long, relatively thin penetrator surrounded by discarding sabot. Two materials lend themselves to penetrator construction: tungsten and depleted uranium, the latter in designated alloys known as staballoys. *Staballoys* are metal alloys of depleted uranium with a very small proportion of other metals, usually titanium or molybdenum. One formulation has a composition of 99.25% by weight of depleted uranium and 0.75% by weight of titanium. Another variant can have 3.5% by weight of titanium. Staballoys are about twice as dense as lead and are designed for use in kinetic energy penetrator armor-piercing ammunition. The US Army uses DU in an alloy with around 3.5% titanium.

Staballoys, along with lower raw material costs, have the advantage of being easy to melt and cast into shape; a difficult and expensive process for tungsten. Depleted uranium is favored for the penetrator because it is self-sharpening and pyrophoric. On impact with a hard target, such as an armoured vehicle, the nose of the rod fractures in such a way that it remains sharp. The impact and subsequent release of heat energy causes it to disintegrate to dust and burn when it reaches air because of its pyrophoric properties (compare to ferrocerium). After a disintegrated DU penetrator reaches the interior of an armored vehicle, it explodes, often igniting ammunition and fuel, incinerating the crew, and causing the vehicle to explode. DU is used by the U.S. Army in 120 mm or 105 mm cannons employed on the M1 Abrams and M60A3 tanks. The Russian military has used DU ammunition in tank main gun ammunition since the late 1970s, mostly for the 115 mm guns in the T-62 tank and the 125 mm guns in the T-64, T-72, T-80, and T-90 tanks.

The DU content in various ammunition is 180 g in 20 mm projectiles, 200 g in 25 mm ones, 280g in 30 mm, 3.5 kg in 105 mm, and 4.5 kg in 120 mm penetrators. It is used in the form of Staballoy. The US Navy used DU in its 20 mm Phalanx CIWS guns, but switched in the late 1990s to armor-piercing tungsten for this application, because of the fire risk associated with stray pyrophoric rounds. DU was used during the mid-1990s in the U.S. to make 9 mm and similar caliber armor piercing bullets, grenades, cluster bombs, and mines, but those applications have been discontinued, according to Alliant Techsystems. Whether or not other nations still make such use of DU is difficult to determine.

It is thought that between 17 and 20 states have weapons incorporating depleted uranium in their arsenals. They include the USA, the UK, France, Russia, Greece, Turkey, Israel, Saudi Arabia, Bahrain, Egypt, Kuwait, Pakistan, Thailand, Iraq and Taiwan. DU ammunition is manufactured in 18 countries. While only the US and the UK have acknowledged using DU weapons, its use by other states cannot be excluded[2].

Legal status in weapons

In 1996 the International Court of Justice (ICJ) gave an advisory opinion on the "legality of the threat or use of nuclear weapons".[3] This made it clear, in paragraphs 54, 55 and 56, that international law on poisonous weapons, – the Second Hague Declaration of 29 July

1899, Hague Convention IV of 18 October 1907 and the Geneva Protocol of 17 June 1925 – did not cover nuclear weapons, because their prime or exclusive use was not to poison or asphyxiate. This ICJ opinion was about nuclear weapons, but the sentence "The terms have been understood, in the practice of States, in their ordinary sense as covering weapons whose prime, or even exclusive, effect is to poison or asphyxiate." also removes depleted uranium weaponry from coverage by the same treaties as their primary use is not to poison or asphyxiate, but to destroy materiel and kill soldiers through kinetic energy.

The Sub-Commission on Prevention of Discrimination and Protection of Minorities of the United Nations Human Rights Commission[4], passed two motions [5] the first in 1996[6] and the second in 1997[7]. They listed weapons of mass destruction, or weapons with indiscriminate effect, or of a nature to cause superfluous injury or unnecessary suffering and urged all states to curb the production and the spread of such weapons. Included in the list was weaponry containing depleted uranium. The committee authorized a working paper, in the context of human rights and humanitarian norms, of the weapons. The requested UN working paper was delivered in 2002[8] by Y.K.J. Yeung Sik Yuen in accordance with Sub-Commission on Promotion and Protection of Human Rights resolution 2001/36. He argues that the use of DU in weapons, along with the other weapons listed by the SubCommission, may breach one or more of the following treaties: The Universal Declaration of Human Rights; the Charter of the United Nations; the Genocide Convention; the United Nations Convention Against Torture; the Geneva Conventions including Protocol I; the Convention on Conventional Weapons of 1980; and the Chemical Weapons Convention. Yeung Sik Yuen writes in Paragraph 133 under the title "Legal compliance of weapons containing DU as a new weapon":

Annex II to the Convention on the Physical Protection of Nuclear Material 1980 (which became operative on 8 February 1997) classifies DU as a category II nuclear material. Storage and transport rules are set down for that category which indicates that DU is considered sufficiently “hot” and dangerous to warrant these protections. But since weapons containing DU are relatively new weapons no treaty exists yet to regulate, limit or prohibit its use. The legality or illegality of DU weapons must therefore be tested by recourse to the general rules governing the use of weapons under humanitarian and human rights law which have already been analysed in Part I of this paper, and more particularly at paragraph 35 which states that parties to Protocol I to the Geneva Conventions of 1949 have an obligation to ascertain that new weapons do not violate the laws and customs of war or any other international law. As mentioned, the ICJ considers this rule binding customary humanitarian law.

In 2001, Carla del Ponte, the chief prosecutor for the International Criminal Tribunal for the Former Yugoslavia, said that NATO's use of depleted uranium in former Yugoslavia could be investigated as a possible war crime[9]. Louise Arbour, del Ponte's predecessor as chief prosecutor, had created a small, internal committee, made up of staff lawyers, to assess the allegation. Their findings, that were accepted and endorsed by del Ponte,[10] concluded that:

There is no specific treaty ban on the use of DU projectiles. There is a developing scientific debate and concern expressed regarding the impact of the use of such projectiles and it is

possible that, in future, there will be a consensus view in international legal circles that use of such projectiles violate general principles of the law applicable to use of weapons in armed conflict. No such consensus exists at present. (Emphasis added)[11]

Civilian applications

Civilian applications for depleted uranium are fairly limited and are typically unrelated to its radioactive properties. It primarily finds application as ballast because of its high density. Such applications include sailboat keels, as counterweights and sinker bars in oil drills, gyroscope rotors, and in other places where there is a need to place a weight that occupies as little space as possible. Other relatively minor consumer product uses have included: incorporation into dental porcelain used for false teeth to simulate the fluorescence of natural teeth; and in uranium-bearing reagents used in chemistry laboratories.

Uranium was widely used as a coloring matter for porcelain and glass in the 19th century. The practice was believed to be a matter of history, however in 1999 concentrations of 10% depleted uranium were found in "jaune no.17" a yellow enamel powder that was being produced in France by Cristallerie de Saint-Paul, a manufacturer of enamel pigments. The depleted uranium used in the powder was sold by Cogéma's Pierrelatte facility. Cogema has since confirmed that it has made a decision to stop the sale of depleted uranium to producers of enamel and glass.

DU is also used for shielding for radiation sources used in medical and industrial radiography.

U.S. Nuclear Regulatory Commission regulations at 10 CFR 40.25 establish mandatory licensing for the use of depleted uranium contained in industrial products or devices for mass-volume applications. Other jurisdictions have similar regulations

Trim weights in aircraft

Aircraft may also contain depleted uranium trim weights (a Boeing 747-100 may contain 400 to 1,500 kg). This application of DU is controversial. If an aircraft crashes there is concern that the uranium would enter the environment: the metal can oxidize to a fine powder in a fire. While arguably other hazardous materials released from a burning commercial aircraft overshadow the contributions made by DU, its use has been phased out in many newer aircraft, Both Boeing and McDonnell-Douglas discontinued using DU counterweights in the 1980s.

Uranium hexafluoride

About 95% of the depleted uranium produced is stored as uranium hexafluoride, (D)UF_6, in steel cylinders in open air yards close to enrichment plants. Each cylinder contains up to 12.7 tonnes (or 14 US tons) of UF_6. In the U.S. alone, 560,000 tonnes of depleted UF_6 had accumulated by 1993. In 2005, 686,500 tonnes in 57,122 storage cylinders were located near Portsmouth, Ohio, Oak Ridge, Tennessee, and Paducah, Kentucky.The long-term storage of

DUF***6*** presents environmental, health, and safety risks because of its chemical instability. When UF***6*** is exposed to moist air, it reacts with the water in the air to produce UO***2***F2 (uranyl fluoride) and HF (hydrogen fluoride) both of which are highly soluble and toxic. Storage cylinders must be regularly inspected for signs of corrosion and leaks. The estimated life time of the steel cylinders is measured in decades.

There have been several accidents involving uranium hexafluoride in the United States. The U.S. government has been converting DUF***6*** to solid uranium oxides for disposal. Such disposal of the entire DUF***6*** inventory could cost anywhere from 15 to 450 million dollars.

Health considerations

The radiological dangers of pure depleted uranium are relatively low, lower (60%) than those of naturally-occurring uranium due to the removal of the more radioactive isotopes, as well as due to its long half-life (4.46 billion years). Depleted uranium differs from natural uranium in its isotopic composition, but its biochemistry is for the most part the same.

Health effects of DU are determined by factors such as the extent of exposure and whether it was internal or external. Three main pathways exist by which internalization of uranium may occur: inhalation, ingestion, and embedded fragments or shrapnel contamination. Properties such as phase (e.g. particulate or gaseous), oxidation state (e.g. metallic or ceramic), and the solubility of uranium and its compounds influence their absorption, distribution, translocation, elimination and the resulting toxicity. For example, metallic uranium is relatively non-toxic compared to hexavalent uranium(VI) compounds such as uranyl nitrate. (See «Gmelin Handbuch der anorganischen Chemiek» 8th edition, English translation, Gmelin Handbook of Inorganic Chemistry, vol. U-A7 (1982) pp. 300-322.)

Uranium is pyrophoric when finely divided. It will corrode under the influence of air and water producing insoluble uranium(IV) and soluble uranium(VI) salts. Soluble uranium salts are toxic. Uranium accumulates in several organs, such as the liver, spleen, and kidneys. The World Health Organization has established a daily "tolerated intake" of soluble uranium salts for the general public of 0.5 µg/kg body weight (or 35 µg for a 70 kg adult.)

The chemical toxicity of uranium salts is greater than their radiological toxicity. Its radiological hazards are dependent on the purity of the uranium, and there has been some concern that depleted uranium produced as a by-product of nuclear reprocessing may be contaminated with more dangerous isotopes: this should not be a concern for depleted uranium produced as tailings from initial uranium enrichment.

Early scientific studies usually found no link between depleted uranium and cancer, and sometimes found no link with increases in the rate of birth defects, but newer studies have and offered explanation of birth defect links. There is no direct proof that uranium causes birth defects in humans, but it induces them in several other species of mammals, and human epidemiological evidence is consistent with increased risk of birth defects in the offspring of persons exposed to DU. Environmental groups and others have expressed concern about the health effects of depleted uranium, and there is significant debate over the matter. Some people have raised concerns about the use of this material, particularly in munitions, because of its proven mutagenicity, teratogenicity in mice, and neurotoxicity, and its suspected carcinogenic potential, because it remains radioactive for an exceedingly long time with a

half-life of approximately 4.5 billion years; and because it is also toxic in a manner similar to lead and other heavy metals.

Early studies of depleted uranium aerosol exposure assumed that uranium combustion product particles would quickly settle out of the air and thus could not affect populations more than a few kilometers from target areas, and that such particles, if inhaled, would remain undissolved in the lung for a great length of time and thus could be detected in urine

By contrast, other studies have shown that DU ammunition has no measurable detrimental health effects, either in the short or long term. The International Atomic Energy Agency reported in 2003 that, "based on credible scientific evidence, there is no proven link between DU exposure and increases in human cancers or other significant health or environmental impacts," although "Like other heavy metals, DU is potentially poisonous. In sufficient amounts, if DU is ingested or inhaled it can be harmful because of its chemical toxicity. High concentration could cause kidney damage."

In October, 1992, an El Al Boeing 747-F cargo aircraft crashed in a suburb of Amsterdam. After reports of local residents and rescue workers complaining of health issues related to the release of depleted uranium used as counterbalance in the plane, authorities began an epidemiological study in 2000 of those believed to be affected by the accident. The study concluded that because exposure levels were so low, it was highly improbable that exposure to depleted uranium was the cause of the reported health complaints.

Gulf War syndrome

Increased rates of immune system disorders and other wide-ranging symptoms have been reported in combat veterans of the 1991 Gulf War. It has not always been clear whether these were related to Gulf War service, but combustion products from depleted uranium munitions is still being considered as a potential cause by the Research Advisory Committee on Gulf War Veterans' Illnesses, as DU was used in tank kinetic energy penetrator and machine-gun bullets on a large scale for the first time in the Gulf War.

Most experts in health physics consider it unlikely that depleted uranium has any connection with the Gulf War Syndrome if such an illness exists at all. A two year study headed by Sandia National Laboratories' Al Marshall analyzed potential health effects associated with accidental exposure to depleted uranium during the 1991 Gulf War. Marshall's study concluded that the reports of serious health risks from DU exposure are not supported by veteran medical statistics and were consistent with earlier studies from Los Alamos and the New England Journal of Medicine [12].

Footnotes

1. ^ Doug Rokke Depleted Uranium: Uses and Hazards (PDF) an updated version of the paper presented in the British House of Commons on December 16, 1999
2. ^ The International Legality of the Use of Depleted Uranium Weapons: A Precautionary Approach, Avril McDonald, Jann K. Kleffner and Brigit Toebes, eds. (TMC Asser Press Fall-2003)

3. ^ legality of the threat or use of nuclear weapons

4. ^ Citizen Inspectors Foiled in Search for DU Weapons

5. ^ Depleted Uranium UN Resolutions

6. ^ Sub-Commission resolution 1996/16

7. ^ Sub-Commission resolution 1997/36

8. ^ E/CN.4/Sub.2/2002/38 Human rights and weapons of mass destruction, or with indiscriminate effect, or of a nature to cause superfluous injury or unnecessary suffering (backup) "In its decision 2001/36 of 16 August 2001, the SubCommission, recalling its resolutions 1997/36 and 1997/37 of 28 August 1997, authorized Mr. Y.K.J. Yeung Sik Yuen to prepare, without financial implications, in the context of human rights and humanitarian norms, the working paper originally assigned to Ms. Forero Ucros."

9. ^ The Associated Press & Reuters contributed to this report: Use of DU weapons could be war crime CNN January 14, 2001

10. ^ *Joe Sills* **et al** Environmental Crimes in Military Actions and the International Criminal. Court(ICC)-United Nations Perspectives *(PDF) (*HTML*) of American Council for the UN University, April 2002. Page 28*

11. ^ The Final Report to the Prosecutor by the Committee Established to Review the NATO Bombing Campaign Against the Federal Republic of Yugoslavia: Use of Depleted Uranium Projectiles

12. ^ An Analysis of Uranium Dispersal and Health Effects Using a Gulf War Case Study**, Albert C. Marshall, Sandia National Laboratories**

Rubella

Classifications and external resources

ICD-10

B06.

ICD-9

056

Rubella virus

Virus classification

Group: Group IV ((+)ssRNA)Family: Togaviridae
Genus: Rubivirus
Species: *Rubella virus*

Rubella (also known as *epidemic roseola*, *German measles*, *liberty measles*[1] or *three-day measles*) is a disease caused by the *Rubella virus*. It is often mild and an attack can pass unnoticed. However, this can make the virus difficult to diagnose. The virus usually enters the body through the nose or throat. The disease can last 1-5 days. Children recover more quickly than adults. Like most viruses living along the respiratory tract, it is passed from person to person by tiny droplets in the air that are breathed out. Rubella can pose a serious risk as it can also be transmitted from a mother to her developing baby through the bloodstream via the placenta. If the mother is infected within the first 20 weeks of pregnancy, the baby will have congenital rubella syndrome. The virus has an incubation period of 2 to 3 weeks during which it becomes established.

The name *German measles* has nothing to do with Germany. It comes from the Latin germanus, meaning "similar", since rubella and measles share many symptoms.

Symptoms

Symptoms of rubella include:
Children: Low grade fever, swollen glands, joint pain, headache, conjunctivitis, rash
Adults and children:

- swollen glands or lymph nodes (may persist for up to a week)
- fever (rarely rises above 38 degrees Celsius [100.4 degrees Fahrenheit])
- rash (Appears on the face and then spreads to the trunk and limbs. It appears as pink dots under the skin. It appears on the first or third day of the illness but it disappears after a few days with no staining or peeling of the skin)
- Forchheimer's sign occurs in 20% of cases, and is characterized by small, red papules on the area of the soft palate
- flaking, dry skin
- nerves become weak or numb (very rare)

Risks

Rubella can affect anyone of any age and is generally a mild disease. However, rubella can cause congenital rubella syndrome in the fetus of an infected pregnant woman.

Prevention and treatment

Symptoms are usually treated with paracetamol until the disease has run its course. There is no treatment available for congenital rubella.

Fewer cases of rubella occur since a vaccine became available in 1969, although decreased uptake of the MMR vaccine (e.g. in the UK) is expected to lead to a rise in incidence. In most Western countries, the vast majority of people are vaccinated against rubella as children at 12 to 15 months of age. A second dose is required before age 11. The vaccine gives lifelong protection against rubella. A side-effect of the vaccine can be transient arthritis.

The immunization program has been quite successful with Cuba declaring the disease eradicated in the 1990s and the United States eradicating it in 2005 [1]. Every minister of health in the Americas plans to eliminate the disease by 2010.

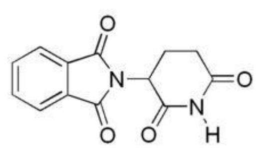
Rubella in popular culture

Agatha Christie's The Mirror Crack'd from Side to Side features a plot, possibly based on real life, in which a girl is shut up in quarantine for a minor illness but climbs out of the window to meet a celebrity. The celebrity is pregnant and unknowingly catches rubella resulting in a child with congenital rubella syndrome. However, as this is the fan's favourite anecdote, when she meets the celebrity years later she tells her this story so the celebrity realises that her baby's retardation were caused by this fan.

References

1. ^ Over Here: World War I on the Home Front. *Digital History*. **Retrieved on 2006-07-12.**

Thalidomide



Systematic (IUPAC) name

2-(2,6-dioxo-3-piperidyl)isoindole-1,3-dione

Identifiers

CAS number 50-35-1

ATC code L04**AX02**

PubChem 5426

DrugBank APRD01251

Chemical data

Formula $C_{13}H_{10}N_2O_4$

Mol. weight 258.23 g/mol

Pharmacokinetic data

Protein binding 55% and 66% for the (+)R and (−)S enantiomers, respectively

Half life mean ranges from approximately 5 to 7 hours following a single dose; not altered with multiple doses

Therapeutic considerations

Pregnancy cat. $X_{(AU)}$ $X_{(US)}$

Legal status Prescription only

Routes oral

Thalidomide is a sedative, hypnotic, and anti-inflammatory medication. It was sold from 1957 to 1961 in almost fifty countries under at least forty names, including Distaval, Talimol, Nibrol, Sedimide, Quietoplex, Contergan, Neurosedyn, and Softenon. Thalidomide was chiefly sold and prescribed during the late 1950s and 1960s to pregnant women, as an antiemetic to combat morning sickness and as an aid to help them sleep. Unfortunately, inadequate tests were performed to assess the drug's safety, with catastrophic results for the children of women who had taken thalidomide during their pregnancies.

From 1956 to 1962, approximately 10,000 children were born with severe malformities, including phocomelia, because their mothers had taken thalidomide during pregnancy.[1] In 1962, in reaction to the tragedy, the United States Congress enacted laws requiring tests for safety during pregnancy before a drug can receive approval for sale in the U.S.[2] Other countries enacted similar legislation, and thalidomide was not prescribed or sold for decades.

Researchers, however, continued to work with the drug. Soon after its banishment, a doctor discovered anti-inflammatory effects of thalidomide and began to look for uses of the medication despite its teratogenic effects. He found that patients with erythema nodosum leprosum, a painful skin condition associated with leprosy, experienced relief of their pain by taking thalidomide. Currently, there are studies underway to determine the drug's effects on arachnoiditis, Crohn's disease, and several types of cancers. However, physicians and patients alike must go through a special process to prescribe and receive thalidomide, to ensure no more children are born with birth defects traceable to the medication.

History

Discovery and introduction

A small German pharmaceutical company, Chemie Grünenthal, synthesized thalidomide in West Germany in 1953 while searching for an inexpensive method of manufacturing antibiotics from peptides. By heating phthaloyisoglutamine, the company's chief researcher produced phthalimidoglutarimide, which they soon labeled 'thalidomide.' Chemie Grünenthal patented the molecule and began searching for a disease thalidomide could cure.[3]

The Grünenthal scientists could not find any antibiotic activity, or any other encouraging effects, in mice and rats. However, they saw that the new chemical seemed to be harmless; outrageously high doses did not kill rodents, rabbits, cats, or dogs. In addition, the animals showed no other side effects. The research team began to describe thalidomide as "nontoxic," and Grünenthal began to consider the lucrative prospects of their new find. Notably, although no sedative or tranquilizing effects were observed in animals, Grünenthal management considered "a nonlethal sedative would have enormous market potential." [3]

With only these animal tests, no clinical trial plans, and no scientific rationale, Grünenthal began distributing free samples of thalidomide to doctors in Switzerland and West Germany in 1955. It was first recommended for the prevention of seizures in patients with epilepsy; although no anticonvulsant effect was found, patients reported experiencing a deep sleep. Other patients said they felt calming and soothing effects. Some reported side effects, but they were not believed to be serious.[3] One author later said that "Thalidomide was introduced by the method of Russian Roulette. Practically nothing was known about the drug at the time of its marketing."[4]

Thalidomide could not be sold in West Germany until its effects on animals were documented – usually effects of a drug are demonstrated on animals before the drug is administered to humans, but thalidomide was not tested that way. The sedative effects had not been seen in animals, so the Grünenthal scientists came up with a "jiggle cage" to measure the movements of mice to see if treated mice "jiggled" the cage less than non-treated mice. Grünenthal also pointed out that their "powerful hypnotic drug was completely safe.[3]

An employee of Chemie Grünenthal brought home samples of the new drug for his pregnant wife, and ten months before thalidomide was put on the market in Germany, on Christmas Day in 1956, their child was born – without ears. Years later, the father learned that his daughter was the first living victim of the epidemic of thalidomide-induced infant malformations and deaths.[3]

The company began selling the drug over the counter in Germany in October 1957, under the brand name Contergan. The company claimed that "Even a determined suicide could not take enough Contergan to cause death" and "accidental overdoses by children would be unheard of with this drug." Soon the drug was being sold in 46 countries under "at least 37 names,"[3] without any additional independent testing, and was the drug of choice for pregnant women with morning sickness.[5] Not one of those statements turned out to be true.

Frances Kelsey

By 1960, Grünenthal was selling thalidomide tablets all over the world – except in the United States. A Cincinnati, Ohio company called Richardson-Merrell tried to change that in

September 1960, when it applied for Food and Drug Administration (FDA) approval to sell thalidomide in the United States under the brand name of Kevadon. The company wanted to begin sales of Kevadon in early 1961. This approval was not expected to be controversial, and the case was given to the agency's newest reviewer, Frances Oldham Kelsey, who had joined the FDA only one month before.

At the time, the prevailing US law was the 1938 Federal Food, Drug, and Cosmetic Act, which required proof of safety be sent to the FDA before a medication could be approved for sale in the United States. The law did *not* require demonstration of efficacy for approval. It also allowed "investigational" or "experimental" use of a drug while approval for its sale was being sought, meaning that a medication could be widely distributed before it was approved.[6] The law gave the FDA 60 days to review a drug application. If the FDA reviewer told a drug company that its application for a particular medication was incomplete, it was considered withdrawn and the company would have to submit more data when it resubmitted the application. With each resubmission, the 60 days started all over again.[1]

This was Kelsey's first drug review assignment for the FDA. She was interested in fetal safety because in the 1940s she had studied quinine, including its effects in pregnancy, while she was part of a team that was trying to find a synthetic cure for malaria. In particular, she recalled a study she conducted on rabbits at the University of Chicago. In that study, she noted that adult rabbits metabolized quinine rapidly, but pregnant rabbits were less able to metabolize it and embryonic rabbits could not metabolize it at all. In addition, contrary to the prevailing theories of the time, Kelsey found that the drug passed through the placental barrier between mother and fetus.[5] Recalling her work with quinine, Kelsey thought that perhaps thalidomide acted the same way – if so, thalidomide might be safe for older, non-pregnant patients, but could be toxic to children, pregnant women and their fetuses.

Kelsey had other worries about thalidomide as well. She wanted to know about the drug's mechanism of action – its effects on human metabolism, its chemistry and pharmacology, and its stability.[2] However, none of this data had been provided by Richardson-Merrell. There had been no chronic toxicity studies, excretion and absorption data was inadequate, and there were few manufacturing controls in place to assure quality.

Kelsey rejected the application and requested the aforementioned data from the company in a letter. Richardson-Merrell resubmitted the application but with no new information, and Kelsey turned it down again. She continued to request more data from the company, and with each request the 60 day clock was rewound to its beginning. As the end of 1960 approached, and with it the holiday season (the best time for selling sedatives)[3], Richardson-Merrell began ratcheting up the pressure on the FDA and Kelsey. Executives and scientists telephoned and personally visited Kelsey, and executives complained to her superiors that she was nit-picking and unreasonable.[1][5]

Still, Kelsey refused to clear Kevadon for sale in the United States until she could review satisfactory studies. She later said that the reports submitted by Grünenthal and Richardson-Merrell were more like testimonials than results of well-designed, controlled studies.[1] (One possible reason for the lack of data could be that Richardson-Merrell's "investigation" of thalidomide for its FDA application was organized and implemented not by scientists, but by the company's sales and marketing division.)[3] It wasn't enough to know how the drug acted in animals – she wanted to know how it worked in humans, and the data was not forthcoming. Kelsey had also heard anecdotal reports of peripheral neuropathy as a side

effect of thalidomide, which only made her think more about the possible effects on a fetus. She continued to reject the Kevadon application. In total, the company resubmitted its Kevadon application to the FDA six times, but no new evidence was given in those applications and Kelsey refused to budge.

Tragedy

Unusual side effects had been reported by patients taking thalidomide in the UK, including peripheral neuropathy. Worse, pregnant women who had taken the drug were giving birth to babies with a condition called phocomelia – abnormally short limbs with toes sprouting from the hips and flipper-like arms. Other infants had eye and ear defects or malformed internal organs such as unsegmented small or large intestines. Chemie Grünenthal denied that thalidomide was responsible for any of these problems. In 1959, Grünenthal responded to one doctor's inquiry by saying, "We have no idea how these cases... could have been caused by Contergan."[3]

Under US law at the time, Richardson-Merrell had been legally distributing Kevdon on an "investigational" basis since early 1960, and pregnant women were included as patients after the first three months of the trial. American doctors were told,[3]

"We have firmly established the safety, dosage, and usefulness of Kevadon by both foreign and US laboratory and clinical studies. This program is designed to obtain widespread confirmation of its usefulness in a variety of hospitalized patients. Doctors need not report results if they don't want to..."

In December 1960, three months after Richardson-Merrell applied for FDA approval of Kevadon, the British Medical Journal published a letter from a British physician who reported cases of peripheral neuropathy, or painful extremities, in patients who had taken thalidomide over a long period of time. Kelsey read this letter, and she believed it was the first indication of toxicity effects.[5] It increased her misgivings about approving the application, and she immediately requested information from Richardson-Merrell about the problem. The company denied knowing about any harmful side effects. Years later, it was shown that Richardson-Merrell knew about the risk of nerve damage but failed to disclose the fact to the FDA.[3] Throughout 1961, more unofficial, anecdotal reports of thalidomide side effects surfaced in Europe and Australia.

On November 18, 1961, the German paper Welt am Sonntag published a letter by German pediatrician Widukind Lenz.[6] Lenz described more than 150 infants with malformations, including phocomelia, and associated them with thalidomide given to their mothers.[3] A stunning statistic was that 50 percent of the mothers with deformed children had taken thalidomide during the first trimester of pregnancy.[1] The limits of danger were amazingly narrow: women who took even one tablet of thalidomide between the 20th and 36th day after conception were at risk for delivering malformed infants – beyond that time, the drug caused no deformities at all.[3] Lenz notified Chemie Grünenthal about the dangers of its flagship product; ten days later, German authorities removed thalidomide from the market against Grünenthal's wishes. Grünenthal withdrew thalidomide soon afterward from the market and notified Richardson-Merrell of its decision.

In December, The Lancet published a letter by William McBride, an Australian physician, who noted large numbers of birth defects in the children of women who had taken thalidomide.[7] Other countries quickly pulled the drug from their stores and pharmacies. However, Grünenthal continued to dispute the claims that thalidomide was responsible for the defects, saying that their action was "merely a response to the sensationalism."[3]

Richardson-Merrill withdrew its Kevadon application in March 1962, but the sheer number and variety of brand names meant the drug remained available in some countries – thalidomide could be found in Brazil, Italy, and Japan as long as nine months after the German withdrawal.[8]

Unfortunately, Grünenthal's decision was too late for thousands of families. An estimated 8,000 to 12,000 infants were born with deformities caused by thalidomide, and of those only about 5,000 survived beyond childhood.[3] The medication never received approval for sale in the United States, but 2.5 million tablets had been given to more than 1,200 American doctors during Richardson-Merrell's "investigation," and nearly 20,000 patients received thalidomide tablets, including several hundred pregnant women. In the end, 17 American children were born with thalidomide-related deformities.[1] An estimated 40,000 people developed drug-induced peripheral neuropathy. Exact numbers will never be known because the companies and doctors kept incomplete and inaccurate records. Fortunately, no thalidomide victims have passed defects to their children, because thalidomide is not a mutagen.[9]

The ensuing American media coverage of thalidomide children, and the woman who refused to approve the drug for use in the United States, enveloped Kelsey and the FDA. Kelsey was praised in a story by Morton Mintz in The Washington Post on July 15, 1962. The headline read, " 'Heroine' of FDA Keeps Bad Drug Off of Market." Follow-up articles appeared in The New York Times, Life magazine, Saturday Review, and hundreds of other publications of the day.

More importantly, a controversial bill by U.S. Senator Estes Kefauver, of Tennessee, was resurrected and rewritten, passed by Congress, and signed by President John F. Kennedy on October 10, 1962. The Kefauver Harris Amendment strengthened the FDA's control of experimentation on humans and changed the way new drugs were approved and regulated. Before the thalidomide scandal, U.S. drug companies only had to show their new products were safe; for the first time, they would have to show their new drugs were safe and effective.[6] Informed consent was required of patients participating in clinical trials, and adverse drug reactions were required to be reported to the FDA.

The legal mess caused by the effects of thalidomide, and Chemie Grünenthal's shoddy testing and approval procedures, is still winding its way through courts worldwide even 50 years later. In connection with one of the first lawsuits, a court-ordered gag rule prohibited all mention of the thalidomide effects for ten years, from 1962 to 1972.[3] In one of the more recent developments in 2003, the Swedish government authorized an ex gratia compensation of SEK 250,000 for each of the 150 individuals that were subjected to thalidomide (marked in Sweden as Neurosedyn). According to a widely disputed investigation by the Swedish Office of the Chancellor of Justice (Justitiekanslern), no blame falls on the Swedish government. The Swedish government later decided to raise the compensation to SEK 500,000 each.

Thalidomide today

FDA Approval

"On May 26, 2006, the U.S. Food and Drug Administration granted accelerated approval for thalidomide (Thalomid, Celgene Corporation) in combination with dexamethasone for the treatment of newly diagnosed multiple myeloma (MM) patients.".htm Incredibly, the FDA approval came seven years after the first reports of efficacy in the medical literature (Desikan R, Munshi N, Zeldis J, et al. Activity of thalidomide (THAL) in multiple myeloma (MM) confirmed in 180 patients with advanced disease. Blood 1999;94:Suppl 1:603a-603a.abstract), and Celgene took advantage of "off-label" marketing opportunities to promote the drug in advance of its FDA approval for the myeloma indication. Thalomid, as the drug is commercially known, sold $300 million plus per year, while only approved for leprosy! [2] Thalidomide was and still is (2006) an important advance in the treatment of multiple myeloma, ever since news of its efficacy spread throughout the medical literature in 2000. The drug has some bothersome nuisance side effects such as neuropathy, constipation, and fatigue, but is likely more effective than chemotherapy for multiple myeloma. Thalidomide, along with another new drug, bortezomib, are changing the landscape of multiple myeloma treatment, such that toxic stem cell transplants may no longer be the standard treatment for this incurable malignancy.

Possible indications

Research on thalidomide slowed in the 1960s, but never completely stopped. The medication is now an example of how potentially dangerous chemical compounds can be used therapeutically with appropriate precautions and procedures.

In 1964, an Israeli physician named Jacob Sheskin was trying to help a critically-ill French patient with erythema nodosum leprosum (ENL), a very painful complication of leprosy. He looked throughout his small hospital for anything that might help his patient stop aching long enough to sleep. He came across a bottle of thalidomide tablets, and remembered that the drug had been effective in helping mentally ill patients sleep – and also that it was banned. Thinking he had nothing to lose, Sheskin gave the man two tablets of thalidomide. The patient slept for hours, and he felt good enough to get out of bed without aid when he woke up. The result was soon followed by more favorable experiences, followed by a clinical trial. Dr. Sheskin's drug of last resort revolutionized the care of leprosy, and led to the closing of most leprosy hospitals.[3]

Serious infections including sepsis and tuberculosis cause the level of tumor necrosis factor ± (TNF±) to rise. TNF± is a chemical mediator in the body, and it may enhance the wasting process in cancer patients as well. Thalidomide may reduce the levels of TNF±, and it is possible that the drug's effect on ENL is caused by this mechanism.[2]

Thalidomide also has potent anti-inflammatory effects that may help ENL patients. In July 1998, the FDA approved the application of Celgene to distribute thalidomide under the brand name Thalomid for treatment of ENL. Celgene received approval for its use against multiple

myeloma in Australia in 2003 and in the US in 2005. [6] Thalomid, in conjunction with dexamethasone, is now standard therapy for multiple myeloma.

Thalidomide also inhibits the growth of new blood vessels (angiogenesis), which may be useful in treating macular degeneration and other diseases; this effect also helps AIDS patients with Kaposi's sarcoma, although there are better and cheaper drugs to treat the condition. Also for AIDS patients, thalidomide may be able to fight painful, debilitating aphthous lesions in the mouth and esophagus which prevent sufferers from eating. The FDA formed a Thalidomide Working Group in 1994 to provide consistency between its divisions, with particular emphasis on safety monitoring. The agency also imposed severe restrictions on the distribution of Thalomid through the System for Thalidomide Education and Prescribing Safety (STEPS) program.[2]

Thalidomide is also being investigated for treating symptoms of prostate cancer, glioblastoma, lymphoma, arachnoiditis, Behçet's disease, and Crohn's disease. In a small trial, Australian researchers found thalidomide sparked a doubling of the number of T cells in patients, allowing the patients' own immune system to attack cancer cells.

Teratogenic mechanism

Thalidomide is racemic – it contains both left- and right-handed isomers in equal amounts. One enantiomer is effective against morning sickness. The other is teratogenic, and causes birth defects. The enantiomers are converted to each other in vivo – that is, if a human is given (R)-thalidomide or (S)-thalidomide, both isomers can be found in the serum – therefore, administering only one enantiomer will not prevent the teratogenic effect in humans.

The mechanism by which thalidomide causes birth defects is not completely understood, although recent papers suggest that it alters TNF± production, modulates integrins, alters T-cell ratios and inhibits angiogenesis. It is known to intercalate into DNA at guanine sites, which may alter expression of certain genes thereby causing the dramatic malformations.

Side effects

Apart from its infamous tendency to induce birth defects and peripheral neuropathy, the main side effects of thalidomide include fatigue and constipation. It also is associated with an increased risk of deep vein thrombosis especially when combined with dexamethasone, as it is for treatment of multiple myeloma. High doses can lead to pulmonary edema, atelectasis, aspiration pneumonia, and refractory hypotension.

Thalidomide analogs

The exploration of the antiangiogenetic and immunomodulatory activities of thalidomide has led to the study and creation of thalidomide analogs. In 2005, Celgene received FDA approval for lenalidomide (Revlimid) as the first commercially useful derivative. Revlimid is only available in a restricted distribution setting to avoid its use during pregnancy. Further studies are conducted to find safer compounds with useful qualities. Another analog,

Actimid, is in the clinical trial phase. These thalidomide analogs can be used to treat different diseases, or used in a regimen to fight two conditions.

Notable children of thalidomide

- Theresia Degener, a prominent human rights lawyer with a special interest in the rights of the disabled
Mat Fraser, a comedian, actor, co-presenter of the BBC's Ouch Podcast
Alvin Law, a motivational speaker and former radio broadcaster.
Tony Melendez is a guitarist who was born without arms. He plays only with his feet.
Brett Nielsen , a musician, was the first Australian thalidomide child
Thomas Quasthoff is an internationally acclaimed bass-baritone who describes himself : "1.34 meters tall, short arms, seven fingers - four right, three left - large, relatively well formed head, brown eyes, distinctive lips; profession: singer."

Thalidomide in literature, music & arts

- On Giant's Shoulders: The Story of Terry Wiles (ISBN 0-7230-0146-4) by Marjorie Wallace, a book & movie about the life of Terry Wiles
Peter Milligan and Brendan McCarthy's short graphic novel Skin (1992) features a teenage skinhead who is a child of thalidomide.
The horror movie Scanners deals with children whose mothers took a similar "wonder drug" during their pregnancy with even more dramatic side effects.
The Punk rock band NOFX wrote a song entitled "Thalidomide Child".
The song "We Didn't Start the Fire" by Billy Joel mentions thalidomide.
The novel Mount Dragon by Douglas Preston and Lincoln Child contains a computer hacker character named Mime who is a thalidomide survivor.
The poem Thalidomide by Sylvia Plath
The novel All Families are Psychotic' by Douglas Coupland refers to thalidomide.
The short story Fortune's Always Hiding by Irvine Welsh in the novel Ecstasy: Three Tales of Chemical Romance (1996) is a story of revenge-seeking thalidomide victims.

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Vitamins

Vitamins are nutrients required in very small amounts for essential metabolic reactions in the body [1]. The term vitamin does not encompass other essential nutrients such as dietary minerals, essential fatty acids, or essential amino acids. Nor does the term refer to the large number of other nutrients that promote health, but are not strictly essential.

Vitamins act both as catalysts and substrates in chemical reactions. When acting as a catalyst, vitamins are bound to enzymes and are called cofactors, for example vitamin K forms part of the proteases involved in blood clotting. Vitamins also act as coenzymes to carry chemical groups between enzymes, for example folic acid carries various forms of carbon groups (methyl, formyl or methylene) in the cell.

Until the 1900s, vitamins were obtained solely through food intake. Many food sources contain different ratios of vitamins. Therefore, if the only source of vitamins is food, a seasonal, yearly or even daily change in diet also alters the ratio of ingested vitamins. Many vitamins can be stored by the body over a range of dosages and short term deficiencies (e.g. during a particular food growing season), do not always result in disease.

Vitamins have been produced as commodity chemicals and made widely available as inexpensive pills for several decades[2] allowing for consistent supplementation to dietary intake.

History

The value of eating certain foods to maintain health was recognized long before vitamins were identified. The ancient Egyptians knew that feeding a patient liver would help cure night blindness, now known to be caused by a vitamin A deficiency. In 1747, the Scottish surgeon James Lind discovered that citrus foods helped prevent scurvy, a particularly deadly disease in which collagen is not properly formed, and is characterized by poor wound healing, bleeding of the gums, and severe pain.[3] In 1753, Lind published his Treatise on the Scurvy, which recommended using lemons and limes to avoid scurvy, which was adopted by the British Royal Navy. This led to the nickname Limey for sailors of that organization. Lind's discovery, however, was not widely accepted by individuals in the Royal Navy's Arctic expeditions in the 19th century, where it was widely believed that scurvy could be prevented by practicing good hygiene, regular exercise, and by maintaining the morale of the crew while on board, rather than by a diet of fresh food.[3] As a result, Arctic expeditions continued to be plagued by scurvy and other deficiency diseases. In the early 20th century, when Robert Falcon Scott made his two expeditions to the Antarctic the prevailing medical theory was that scurvy was caused by "tainted" canned food.[3]

In 1881, Russian surgeon Nikolai Lunin studied the effects of scurvy while at the University of Tartu (in present day Estonia).[4] He fed mice an artificial mixture of all the separate constituents of milk known at that time, namely the proteins, fats, carbohydrates, and salts. The mice that received only the individual constituents died, while the mice fed by milk itself developed normally. He made a conclusion that "a natural food such as milk must therefore contain, besides these known principal ingredients, small quantities of unknown substances essential to life".[4] However, his conclusions were rejected by other researchers

when they were unable to reproduce his results. One difference was that he had used table sugar (sucrose), while other researchers had used milk sugar (lactose) which still contained small amounts of vitamin B.

In 1897, Christiaan Eijkman discovered that eating unpolished rice instead of the polished variety helped to prevent the disease beriberi. The following year, Frederick Hopkins postulated that some foods contained "accessory factors"—in addition to proteins, carbohydrates, fats, etc.—that were necessary for the functions of the human body.[3] Hopkins was awarded the 1929 Nobel Prize for Physiology or Medicine, with Christiaan Eijkman, for their discovery of several vitamins.

Kazimierz Funk was the first to isolate the water-soluble complex of micronutrients, whose bioactivity Fletcher had identified, and Funk proposed the complex be named "Vitamine".[5] The name soon became synonymous with Hopkins' "accessory factors", and by the time it was shown that not all vitamins were amines, the word was already ubiquitous. In 1920, Jack Cecil Drummond proposed that the final "e" be dropped, to deemphasize the "amine" reference, after the discovery that vitamin C had no amine component.

Throughout the early 1900s, the use of deprivation studies allowed scientists to isolate and identify a number of vitamins. Initially, lipid from fish oil was used to cure rickets in rats, and the fat-soluble nutrient was called "antirachitic A". The irony here is that the first "vitamin" bioactivity ever isolated, which cured rickets, was initially called "vitamin A", the bioactivity of which is now called vitamin D,[6] What we now call "vitamin A" was identified in fish oil because it was inactivated by ultraviolet light.

In 1931, Albert Szent-Györgyi and his research fellow Joseph Svirbely, determined that "hexuronic acid" was actually vitamin C and noted its anti-scorbutic activity, and 1937 Szent-Györgyi was awarded the Nobel Prize for his discovery. In 1943 Edward Adelbert Doisy and Henrik Dam were awarded the Nobel Prize for their discovery of vitamin K and its chemical structure.

Human vitamins

Vitamins are classified as either water soluble, meaning that they dissolve easily in water, or fat soluble, and are absorbed through the intestinal tract with the help of lipids. Each vitamin is typically used in multiple reactions and therefore, most have multiple functions.[7]

In humans there are thirteen vitamins, divided into two groups; four fat-soluble vitamins (A, D, E and K), and nine water-soluble vitamins (eight B vitamins and vitamin C).

Vitamin name: Chemical name / Solubility / Deficiency disease / Recommended Dietary Allowances (male, age 19–70) / Upper Intake Level (UL/day)

Vitamin A

Retinoids (include: retinol, retinal, retinoic acid, 3-dehydroretinol and its derivatives) / Fat Night-blindness, Keratomalacia[9] / *900 µg /* 3,000 µg

Vitamin B1

Thiamine / Water / Beriberi / *1.2 mg* / (N/D)[10]

Vitamin B2

Riboflavin / Water / Ariboflavinosis / *1.3 mg* / N/D

Vitamin B3

Niacin / Water / Pellagra / *16.0 mg* / 35.0 mg

Vitamin B5

Pantothenic acid / Water / Paresthesia / 5.0 mg [11] / N/D

Vitamin B6

Pyridoxine / Water / Anemia[12] / *1.3-1.7 mg* / 100 mg

Vitamin B7

Biotin / Water / n/a / 30.0 µg / N/D

Vitamin B9

Folic acid / Water / Deficiency during pregnancy is associated with birth defects. / *400 µg* / 1,000 µg

Vitamin B12

Cyanocobalamin / Water / Megaloblastic anaemia[13] / *2.4 µg* / N/D

Vitamin C

Ascorbic acid / Water / Scurvy / *90.0 mg* / 2,000 mg

Vitamin D2–D4

Lumisterol, Ergocalciferol, Cholecalciferol, Dihydrotachysterol, 7-Dehydrocholesterol / Fat / Rickets / 5.0 µg-10 µg [14] / 50 µg

Vitamin E

Tocopherol, Tocotrienol / Fat / deficiency is very rare, mild hemolytic anemiain newborn infants [15] / *15.0 mg* / 1,000 mg

Vitamin K

Naphthoquinone (not to be confused with ***ketamine***) / Fat / Bleeding diathesis / 120 µg / N/D

Vitamins in nutrition and disease

Vitamins are essential for normal growth and development. Using the genetic blueprint inherited from its parents, a fetus begins to develop, at the moment of conception, from the nutrients it absorbs.

The developing fetus requires certain vitamins and minerals to be present at certain times. These nutrients facilitate the chemical reactions that produce, among other things, skin, bone, and muscle. If there is serious deficiency in one or more of these nutrients, a child may develop a deficiency disease. Minor deficiencies also have the potential to cause permanent damage, and may be associated with reduced life expectancy.[16]

For the most part, vitamins are obtained through food sources. However, a few vitamins are obtained by other means: for example, microorganisms in the intestine - commonly known as "gut flora" - produce vitamin K and biotin, while one form of vitamin D is synthesized in the skin with the help of natural ultraviolet in sunlight. Some vitamins can be obtained from precursors that are obtained in the diet. Examples include vitamin A, which can be produced from beta carotene and niacin from the amino acid tryptophan.**[8]**

Once growth and development are completed, vitamins remain essential components of the healthy maintenance of the cells, tissues, and organs that make up the human body, and enable the body to efficiently use the calories provided by the food that we eat, and to help process proteins, carbohydrates, and fats.

Vitamin deficiencies

An organism can survive for some time without vitamins, although prolonged vitamin deficits may result in often painful and potentially deadly diseases. Body stores for different vitamins can vary widely; an adult may be deficient in vitamin A and B***12*** for long periods of time before developing a deficiency condition, while vitamin B***3*** stores may only last a couple of weeks.[9][15]

Deficiencies of vitamins are classified as either primary or secondary. A primary deficiency occurs when you do not get enough of the vitamin in the food you eat. A secondary deficiency may be due to an underlying disorder that prevents or limits the absorption or use of the vitamin, or due to a “lifestyle factor”, such as smoking, excessive alcohol consumption, or the use of medications that interfere with the absorption or the body's use of the vitamin.[15]

Well-known vitamin deficiencies involve thiamine (beriberi), niacin (pellagra), vitamin C (scurvy) and vitamin D (rickets). In much of the developed world, such deficiencies are rare due to; an adequate supply of food and the addition of vitamins and minerals, often called fortification, to common foods.[8][15][17]

Vitamin side effects and overdose

Vitamins are classified as fat-soluble or water-soluble based on how they are absorbed by the body. Vitamins A, D, E, and K are fat soluble, while the water-soluble vitamins include vitamin C and the B-complex vitamins (thiamine (B1), riboflavin (B2), niacin (B3), pantothenic acid (B5), vitamin B6, vitamin B12, biotin and folate.

Fat-soluble vitamins (A, D, E and K) are often stored in the body and can cause toxicity when ingested in excess. With the exception of vitamin B12, which is stored in the liver[13], water-soluble vitamins are not stored in the body. All vitamins have documented side effects. Like side effects from drugs, vitamin side effects increase in severity with increasing dosage. At high enough dosages vitamins can cause extreme side effects such as nausea, diarrhea, and vomiting.[8] Unlike side effects caused by drugs, vitamin side effects rarely cause any permanent harm.[18] When vitamin side effects emerge, full and rapid recovery is accomplished by reducing the supplement dosage. Furthermore, the concentrations of vitamins an individual can tolerate vary widely, and appear to be related to age and state of health.[19]

The likelihood of consuming too much of any vitamin from food is remote, but overdosing from vitamin supplementation does occur. It is for this reason that physicians and scientists carefully review all the clinical data on supplement use in order to determine upper dosage thresholds for each vitamin that can be tolerated as a daily dose by the entire population without side effects. This dosage is known as the tolerable upper intake level (UL).[8]

The supplement controversy

Dietary supplements are often used to ensure that adequate amounts on nutrients are obtained on a daily basis, if the nutrients cannot be obtained through a varied diet. Scientific evidence supporting the benefits of some dietary supplements is well established for certain health conditions, but others need further study.[20] It is also important to note that some supplements include vitamins and minerals, as well as herbs, botanicals and other substances.

Supplements are, as required by law, not intended to treat, diagnose, mitigate, prevent, or cure disease.[20] In some cases, dietary supplements may have unwanted effects, especially if taken before surgery, with other dietary supplements or medicines, or if the taker has certain health conditions.[20] Vitamin supplements may also contain levels of vitamins many times higher, and in different forms, than one may ingest through food.[21] Before taking a supplement, it is important to check with a knowledgeable health care provider, especially when combining or substituting supplements with other foods or medicine.

Governmental regulation of vitamin supplements

Most countries place dietary supplements in a special category under the general umbrella of "foods," not drugs. This necessitates that the manufacturer, and not the government, be responsible for ensuring that its dietary supplement products are safe before they are marketed. Unlike drug products, that must implicitly be proven safe and effective for their intended use before marketing, there are often no provisions to "approve" dietary supplements for safety or effectiveness before they reach the consumer. Also unlike drug products, manufacturers and distributors of dietary supplements are not generally required to report any claims of injuries or illnesses that may be related to the use of their products[22] however, side effects have been reported for several types of supplements.[23]

Names in current and previous nomenclatures

The reason the set of vitamins seems to skip directly from E to the rarely-mentioned K is that the vitamins corresponding to "letters" F-J were either reclassified over time, were discarded as false leads, or were renamed because of their relationship to "vitamin B", which became a "complex" of vitamins. The following table lists chemicals that had previously been classified as vitamins, as well as the earlier names of vitamins that later became part of the B-complex.

Previous vitamin name [24] [25]	Chemical name[24][25]	Current vitamin name[24]	Reason for name change[24]
Vitamin B_4	Adenine	N/A	No longer classified as a vitamin
Vitamin B_8	Adenylic acid	N/A	No longer classified as a vitamin
Vitamin F	Essential fatty acids	N/A	Needed in large quantaties, does not fit definition of vitamin.
Vitamin G	Riboflavin	Vitamin B_2	Reclassified as B-complex
Vitamin H/ Vitamin I	Biotin	Vitamin B_7	Reclassified as B-complex
Vitamin J	Catechol, Flavin	N/A	No longer classified as a vitamin
Vitamin L_1	Orthoaminobenzoic acid, Anthranilic acid	N/A	No longer classified as a vitamin
Vitamin L_2	Adenyl thiomethylpentose	N/A	No longer classified as a vitamin
Vitamin M	Folic acid	Vitamin B_9	Reclassified as B-complex
Vitamin P	Flavonoids	N/A	No longer classified as a vitamin
Vitamin PP	Niacin	Vitamin B_3	Reclassified as B-complex
Vitamin R, Vitamin B_{10}	Pteroylmonoglutamic acid	N/A	No longer classified as a vitamin
Vitamin S, Vitamin B_{11}	Pteroylheptaglutamic acid	N/A	No longer classified as a vitamin
Vitamin U	Allantoine	N/A	No longer classified as a vitamin

See also

- Nutrition
  - Nutrients
    - Dietary minerals
    - Essential amino acids
  - Nootropics (cognitive enhancers)
- Dietetics
- Dietary supplement
- Illnesses related to poor nutrition
  - Orthomolecular medicine
- Pharmacology
- Vitamin poisoning (overdose)
  - Health freedom
  - Whole food supplements

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3. **^** a b c d **Jack Challem (1997).** "The Past, Present and Future of Vitamins"
4. **^** a b 1929 Nobel lecture
5. ^ Funk, C. and H. E. Dubin. The Vitamines. Baltimore: Williams and Wilkins Company, 1922.
6. ^ **Bellis, Mary.** Vitamins - Production Methods The History of the Vitamins**. Retrieved 1 Feb 2005.**
7. ^ Kutsky, R.J. (1973). Handbook of Vitamins and Hormones. New York: Van Nostrand Reinhold.
8. ^ a b c d e *f* Dietary Reference Intakes: Vitamins The National Academies, 2001.
9. **^** a b Vitamin and Mineral Supplement Fact Sheets Vitamin A

10. ^ N/D= "Amount not determinable due to lack of data of adverse effects. Source of intake should be from food only to prevent high levels of intake"(see Dietary Reference Intakes: Vitamins).

11. ^ Plain type indicates Adequate Intakes (A/I). "The AI is believed to cover the needs of all individuals, but a lack of data prevent being able to specify with confidence the percentage of individuals covered by this intake" (see Dietary Reference Intakes: Vitamins).

12. ^ Vitamin and Mineral Supplement Fact Sheets Vitamin B***6***

13. **^** a b Vitamin and Mineral Supplement Fact Sheets Vitamin B***12***

14. ^ Value represents suggested intake without adequate sunlight exposure (see Dietary Reference Intakes: Vitamins).

15. ^ ***a*** ***b*** ***c*** ***d*** The Merck Manual: Nutritional Disorders: Vitamin Introduction Please select specific vitamins from the list at the top of the page.

16. ^ **Dr. Leonid A. Gavrilov,** Pieces of the Puzzle: Aging Research Today and Tomorrow

17. ^ Vitamin E Fact sheet

18. ^ Institute of Medicine, Food and Nutrition Board. Dietary Reference Intakes: Calcium, Phosphorus, Magnesium, Vitamin D and Fluoride. National Academy Press, Washington, DC, 1999

19. ^ Healthier Kids [1]

20. ^ ***a*** ***b*** ***c*** Use and Safety of Dietary Supplements NIH office of Dietary Supplements.

21. ^ **Jane Higdon** Vitamin E recommendations at Linus Pauling Institute's Micronutrient Information Center

22. ^ Overview of Dietary Supplements

23. ^ FDA Warnings and Safety information

24. ^ a b c d Every Vitamin Page All Vitamins and Pseudo-Vitamins. Compiled by David Bennett.

25. **^** a b Vitamins and minerals - names and facts

General References Include:

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B vitamins

Vitamin B is a complex of eight water soluble vitamins, active in cell metabolism. The name arises because it was once considered a single vitamin, much like Vitamin C or Vitamin D. Since later research has shown it is in fact a complex of chemically distinct vitamins that happen to often coexist in the same foods, the name has gradually declined in use, being replaced by the generic term *"the B vitamins"*, *the vitamin B complex*, or by the specific names of each vitamin.

List of B vitamins

- Vitamin B1, (Thiamine)

Vitamin B2, (Riboflavin)
Vitamin B3, also Vitamin P or Vitamin PP (Niacin)
Vitamin B5, (Pantothenic acid)
Vitamin B6, (Pyridoxine and Pyridoxamine)
Vitamin B7, also Vitamin H (Biotin)
Vitamin B9, also Vitamin M and Vitamin B-c (Folic acid) - important for pregnancies
Vitamin B12, (Cyanocobalamin)

B vitamins deficiency

Several named vitamin deficiency diseases may result from the lack of sufficient B-vitamins.

- *Vitamin B*1 (Thiamine) deficiency causes Beriberi. Symptoms of this disease of the nervous system include weight loss, emotional disturbances, Wernicke's encephalopathy (impaired sensory perception), weakness and pain in the limbs, periods of irregular heartbeat, and edema (swelling of bodily tissues). Heart failure and death may occur in advanced cases. Chronic thiamine deficiency can also cause Korsakoff's syndrome, an irreversible psychosis characterized by amnesia and confabulation.
- *Vitamin B*2 (Riboflavin) deficiency causes Ariboflavinosis. Symptoms may include cheilosis (cracks in the lips), high sensitivity to sunlight, angular cheilitis, glossitis (inflammation of the tongue), seborrheic dermatitis or pseudo-syphilis (particularly affecting the scrotum or labia majora and the mouth), pharyngitis, hyperemia, and edema of the pharyngeal and oral mucosa.
- *Vitamin B*3 (Niacin) deficiency, along with a deficiency of tryptophan causes Pellagra. Symptoms include aggression, dermatitis, insomnia, weakness, mental confusion, and diarrhea. In advanced cases, pellagra may lead to dementia and death.

Deficiencies of other B vitamins result in symptoms that are not part of a named deficiency disease.

- *Vitamin B*5 (Pantothenic acid) deficiency can result in acne and Paresthesia, although it is uncommon.
- *Vitamin B*6 (Pyridoxine) deficiency may lead to anemia, depression, dermatitis, high blood pressure (hypertension) and elevated levels of homocysteine.
- *Vitamin B*7 deficiency does not typically cause symptoms in adults but may lead to impaired growth and neurological disorders in infants.
- *Vitamin B*9 (Folic acid) deficiency results in elevated levels of homocysteine. Deficiency in pregnant women can lead to birth defects.
- *Vitamin B*12 (Cyanocobalamin) deficiency causes pernicious anemia, memory loss and other cognitive decline. It is most likely to occur among elderly people as absorption through the gut declines with age. In extreme (fortunately rare) cases paralysis can result.

Related nutrients

Other substances which are very similar in structure and function to the B vitamins have been discovered. Many of them are "essential" vitamins to various plants and animals which cannot synthesize their own. (The adjective "essential" in the context of medicine and nutrition refers to a nutrient being required because it cannot be made by the body. Non-"essential" nutrients are still important.) None of these are "essential" vitamins to humans, because humans can synthesize their own, though some only technically so (choline, for instance, can be metabolized in humans by cannibalizing cells to make use of the choline they contain, killing the cells in the process).

Many of the following substances have been referred to as vitamins because they were believed to be vitamins at one time. Most of them are vitamins with respect to certain plants and animals as well. While they are non-"essential" in that they may be synthesized by the body from other starting materials, they are still important.

- Vitamin B***4*** *(*Adenine*)* –
- *Vitamin B*7 "Vitamin I" of Centanni E. (1935) — more commonly called Vitamin B7 and also called 'Enteral factor' is a water and alcohol (ethanol & methanol) soluble Rice bran factor which prevents digestive disterbance in Pigions. It governes the anatomical and functional integrity of the intestineal tract. Later (1945) found in Yeast; Inositol, Nicotinic acid, & Biotin are possibles. Note: Carnitine has also been claimed but is not possible as it is insoluble in alcohol. Carnitine as Vitamin B7 was wrongly coped from Vitamin BT.
- *Vitamin B*8 (Ergadenylic acid) – also known as adenosine monophosphate
- *Vitamin B*10 (para-aminobenzoic acid, or PABA)–
- *Vitamin B*11 (Pteryl-hepta-glutamic acid) – Chick growth factor, which is a form of Folic acid. Later found to be one of five folates necessary for humans); (L-carnitine) in France.

- *Vitamin B*13 (Pyrimidinecarboxylic acid) – Also known as Orotic acid, often misspelled erotic acid.
- *Vitamin B*14 – cell proliferant, anti-anemia, rat growth, an antitumor pterin phosphate named by Earl R. Norris (biochemist of folic acid fame) isolated from human urine at 0.33ppm (later in blood), but later abandoned by him as further evidence did not comfirm this. He also clamed this was not Xanthopterin as the French do.
- *Vitamin B*15 (Pangamic acid) –
- *Vitamin B*16 (dimethylgycine) – also known as DMG. (However Lipoic acid was discovered and named a B-Vitamin after B15 and before B17)
- *Vitamin B*17 (Amygdalin) –
- Vitamin B***18*** –
- Vitamin B***19*** –
- *Vitamin B*20 (Carnitine) –
- Vitamin B***21*** –
- *Vitamin B*22 – often claimed as an ingredient of Aloe vera extracts but also in many other foods. Claimed by one source to be Vitamin B12b-delta. first mentioned on internet in reference to Naturopath Linda Clark's book "Know your Nutrition"
- *Vitamin B*h – another name for(biotin)
- *Vitamin B**m*** ("mouse factor") – also used to designate Inositol
- *Vitamin B*p (Choline) –
- *Vitamin B*t (L-carnitine) –
- *Vitamin B*v – a type of B6 but not Pyrodoxine
- *Vitamin B*w – a type of Biotin but not d-Biotin
- *Vitamin B*x – another name for PABA (para-Aminobenzoic acid)
- Lipoic acid –

Note: *B*16, *B*17, *B*18, *B*19, *B*20, *B*21 & *B*22 do not appear to be animal factors but are claimed by naturopaths as human therapedic factors.

Health benefits

The B vitamins often work together to deliver a number of health benefits to the body. B vitamins have been shown to:

- Bolster metabolism

Maintain healthy skin and muscle tone
Enhance immune and nervous system function
Promote cell growth and division — including that of the red blood cells that help prevent anemia.

Together, they also help combat the symptoms and causes of stress, depression, and cardiovascular disease.

All B vitamins are water soluble, and are dispersed throughout the body. They must be replenished daily with any excess excreted in the urine.

Vitamin B sources

Vitamin B comes from a number of natural sources, including potatoes, bananas, lentils, chili peppers, tempeh, liver, turkey, and tuna. Nutritional yeast (or brewer's yeast) is an especially good source of Vitamin B. The iconic Australian spread Vegemite bills itself as "One of the worlds richest known sources of vitamin B". As might be expected due to its high content of brewer's yeast, beer is a good source of B vitamins, although this may not be true of filtered beers; in fact, beer is sometimes referred to as "liquid bread".

Another popular means of increasing one's Vitamin B intake is through supplements, purchased at supermarkets, health centers, or natural food stores.

References

- Linda Clark's "Know your Nutrition": ISBN 0-87983-401-3

Adenine

Chemical name 9H-Purin-6-amine

Alternate name 6-aminopurine

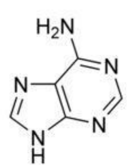
Chemical formula $C_5H_5N_5$

Molecular mass 135.1267 g/mol

Melting point 360 - 365 °C

CAS number 73-24-5

SMILES NC1=NC=NC2=C1N=CN2



Adenine is one of the two purine nucleobases used in forming nucleotides of the nucleic acids DNA and RNA. In DNA, adenine binds to thymine via two hydrogen bonds to assist in stabilizing the nucleic acid structures. In RNA, adenine binds to uracil, which is used in the cytoplasm for protein synthesis.

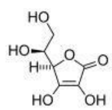
It forms several tautomers, compounds that can be rapidly interconverted and are often considered equivalent. Guanine, a related compounds (also a purine derivative), forms tautomers in the same way, and has more detailed information too.

Adenine forms adenosine, a nucleoside, when attached to ribose, and deoxyadenosine when attached to deoxyribose; it forms adenosine triphosphate (ATP), a nucleotide, when three phosphate groups are added to adenosine. Adenosine triphosphate is used in cellular metabolism as one of the basic methods of transferring chemical energy between chemical reactions.

In older literature, adenine was sometimes called *Vitamin B*4. However it is no longer considered a true vitamin nor part of Vitamin B.

Some think that, at the origin of life on Earth, the first adenine was formed by the polymerizing of five hydrogen cyanide (HCN) molecules. However, this has been criticized by some chemists [1].

Vitamin C


Chemical structure of vitamin C

Vitamin C is a water-soluble nutrient and human vitamin essential for life and for maintaining optimal health, used by the body for many purposes. It is also known by the chemical name of its principal form, L-ascorbic acid. The article on ascorbic acid contains information on its chemical properties. This article describes its biological functions, discovery and the debate on how it is used by society.

General description

Almost all animals and plants synthesize their own vitamin C. There are some exceptions, such as humans and a small number of other animals, including, apes, guinea pigs, the red-vented bulbul, a fruit-eating bat and a species of trout. This has led some scientists, including chemist Linus Pauling to hypothesize that these species either lost (or never had) the ability to produce their own Vitamin C, and that if their diets were supplemented with an amount of the nutrient proportional to the amount produced in animal species that do synthesize their own Vitamin C, better health would result. The species-specific loss of the ability to synthesize ascorbate strikingly parallels the evolutionary loss of the ability to break down uric acid. Uric acid and ascorbate are both strong reducing agents (electron-donors). This has led to the suggestion that in higher primates, uric acid has taken over some of the functions of ascorbate. Acorbic acid can be broken down by *ascorbic acid oxdase* an enzyme which catalyes the oxidation of ascorbic acid.

Some microorganisms such as the yeast Saccharomyces cerevisiae have been shown to be able to synthesize ascorbic acid.

Vitamin C was first isolated in 1928, and in 1932 it was proved to be the agent which prevents scurvy. Both Charles Glen King at the University of Pittsburgh and Albert Szent-Györgyi (working with ex-Pittsburgh researcher Joseph Svirbely) came to discover what is now known as Vitamin C around April of 1932. Although Szent-Györgyi was awarded the

1937 Nobel Prize in Medicine, many feel King is as responsible for its development if not more so.

Vitamin C is a weak acid, called ascorbic acid or a salt ascorbate. It is the L-enantiomer of ascorbic acid. The D-enantiomer shows no biological activity. Both are mirror image forms of the same chemical molecular structure.

The active part of the substance is the ascorbate ion, which can express itself as either an acid or a salt of ascorbate that is neutral or slightly basic. Commercial vitamin C is often a mix of ascorbic acid, sodium ascorbate and/or other ascorbates. Some supplements contain in part the D-enantiomer, which is useless and harmless.

Vitamin C deficiency

No bodily organ stores ascorbate as a primary function, and so the body soon depletes itself of ascorbate if fresh supplies are not consumed through the digestive system, eventually leading to the deficiency disease known as scurvy (a form of avitaminosis), which results in illness and death if consumption of vitamin C is not resumed in time.

Daily requirements and dose dependent effects

There is continuing debate within the scientific community over the best dose schedule (the amount and frequency of intake) of Vitamin C for maintaining optimal health in humans.[1]

Government agency recommended intake levels

A balanced diet without supplementation contains enough Vitamin C to prevent acute scurvy in an average healthy adult. For people who smoke, those under stress, and pregnant women it takes slightly more.

Recommendations for vitamin C intake have been set by various national agencies as follows:

40 mg per day: Food Standards Agency (UK)[2]

60–95 mg per day, Dietary Reference Intake (DRI), Recommended Daily Allowance (RDA), U.S. Food and Nutrition Board 2004.[3]

The U.S. Dietary Reference Intake Tolerable Upper Intake Level (UL) for a 25-year old male is 2,000 mg/day. Vitamin C is recognized to be one of the least toxic substances known to medicine. Its LD50 for rats is 11,900 mg kg^{-1}

Independent dose recommendations

Some researchers have calculated the amount needed for an adult human to achieve similar blood serum levels as Vitamin C synthesising mammals as follows:

400 mg per day – Linus Pauling Institute & US National Institutes of Health (NIH) Recommendation. 500 mg twice per day – Professor Roc Ordman's recommendation in free

radical research. [4] 3000 mg per day or more during illness or pregnancy (up to 300g for some illnesses) – Vitamin C Foundation's recommendation. [5] 6000-12000 mg per day – Thomas Levy, Colorado Integrative Medical Centre recommendation. 6000-18000 mg per day – Linus Pauling's own daily recommendation from 3000 mg to 200,000 mg per day based on a protocol described by Robert Cathcart[6] known as a vitamin C flush wherin escalating doses of Vitamin C are given until diarrhea develops, then choosing the highest dose that does not cause diarrhea (bowel tolerance threshold). High doses (thousands of mg) may result in diarrhea, which is harmless if the dose is reduced immediately. Some researchers[6] claim the onset of diarrhea to be an indication of where the body's true vitamin C requirement lies. Both Cathcart[6] and Cameron have demonstrated that very sick patients with cancer or influenza do not display any evidence of diarrhea at all until ascorbate intake reaches levels as high as 200 grams (½ pound).

There is a strong advocacy movement for large doses of Vitamin C (see Advocacy arguments below), although not all purported benefits are supported by the medical establishment. Many pro-Vitamin C organizations promote usage levels well beyond the current Dietary Reference Intake (DRI).

There exist an extensive and growing literature critical of governmental agency dose recommendations. Key arguments include: [1] [7][8] [9][10] [11][12] [13]

- The biological halflife for vitamin C is quite short, about 30 minutes in blood plasma, a fact which NIH and IM researchers have failed to recognize. NIH researchers established the current RDA based upon tests conducted 12 hours (24 half lives) after consumption. "To be blunt," says Hickey, "the NIH gave a dose of vitamin C, waited until it had been excreted, and then measured blood levels." [14]
- NIH don't take into account individual differences such as age, weight, etc. For example, heavier individuals generally need more vitamin C.
- The figures represent the amount needed to prevent the acute form of deficiency disease, while subclinical levels of the disease are not even acknowledged.
- The amount needed to prevent other diseases is not considered.
- Optimal health is not a consideration, as the level of health targeted is that which is marginally better than that which is considered malnourished.

Therapeutic applications and doses

Vitamin C is needed in the diet to prevent scurvy, however, from the time it became available in pure form in the 1930s, some practitioners experimented with vitamin C as a treatment for diseases other than scurvy.

Colds

At least 29 controlled clinical trials (many double-blind and placebo-controlled) involving a total of over 11,000 participants have been conducted into vitamin C and the

Common cold. These trials were reviewed in the 1990s[15][16] and again recently.[8] The trials show that vitamin C reduces the duration and severity of colds but not the frequency. The data indicate that there is a normal dose-response relationship. Vitamin C is more effective the higher the dose. The vast majority of the trials were limited to doses below 1 g/day. As doses rise, it becomes increasingly difficult to keep the trials double blind because of the obvious gastro-intestinal side effects. So, the most effective trials at doses between 2 and 10 g/day are met with skepticism. Reports from physicians have provided ample clinical confirmation.

The controlled trials and clinical experience prove that vitamin C in doses ranging from 0.1 to 2.0 g/day have a relatively small effect. The duration of colds was reduced by 7% for adults and 15% for children. The studies provide ample justification for businesses to encourage their employees to take 1 to 2 g/day during the cold season to improve workplace productivity and reduce sick days. The clinical reports provide the strongest possible evidence that vitamin C at higher doses is significantly more effective. However, the effectiveness typically comes at the price of gastro-intestinal side effects. It is easy for physicians to minimize these side effects since they cause no lasting harm. Adult patients, however, have proven reluctant to subject themselves to gas and cramping to deliver an unknown benefit (the duration and severity of colds is highly variable so the patient never knows what he/she is warding off). It is well worth the effort of identifying the small subset of individuals who can benefit from high daily doses (>10 g/day) of vitamin C without side effects and training them to regularly take 5 g/day during cold season and to increase the dose at the onset of a cold.

The trials proved that vitamin C is more effective for children. Reports from the field confirm the observations in the trials and suggest that children are less prone to vitamin C side effects Colds and flu are a serious problem for children. Every time a cold infects a child, its growing mind and body must divert energy from its usual business of growth and development. If the cold is followed by an opportunistic infection, such as bronchitis or ear infection, more energy must be diverted. Colds are the number one trigger for asthma. Pre-school children in daycare are nearly constantly fighting infections (5-10 per year). Chronic disease in childhood is believed to sometimes have permanent developmental consequences which can contribute to decreased life expectancy

Polio

Most notable was Fred R. Klenner, a doctor in general practice in Reidsville, North Carolina. He utilized both oral and intravenous vitamin C to treat a wide range of infections and poisons. He published a paper in 1949 that described how he had seen poliomyelitis yield to vitamin C in sufficiently large doses.No controlled clinical trials have been conducted to confirm effectiveness.

Vitamin C is the main of the three ingredients in Linus Pauling's patented preventive cure for heart disease, the other two being the amino acid lysine and nicotinic acid (a form of Vitamin B3). This treatment is not supported by mainstream medical science.

Viral diseases, and poisons

Orthomolecular medicine and a minority of scientific opinion sees vitamin C as being a low cost and safe way to treat viral disease and to deal with a wide range of poisons.

Vitamin C has a growing reputation for being useful in the treatment of colds and flu, owing to its recommendation by prominent biochemist Linus Pauling. In the years since Pauling's popular books about vitamin C, general agreement by medical authorities about larger than RDA amounts of vitamin C in health and medicine has remained elusive. Ascorbate usage in studies of up to several grams per day, however, have been associated with decreased cold duration and severity of symptoms, possibly as a result of an antihistamine effect. The highest dose treatments, published clinical results of specific orthomolecular therapy regimes pioneered by Drs. Klenner (repeated IV treatments, 400-700+ mg/kg/day) and Cathcart (oral use to bowel tolerance,[6] up to ~150 grams ascorbate per day for flu), have remained experimentally unaddressed by conventional medical authorities for decades.

The Vitamin C Foundation recommends an initial usage of up to 8 grams of vitamin C every 20-30 minutes in order to show an effect on the symptoms of a cold infection that is in progress. Most of the studies showing little or no effect employ doses of ascorbate such as 100 mg to 500 mg per day, considered "small" by vitamin C advocates. Equally importantly, the plasma half life of high dose ascorbate is approximately 30 minutes, which implies that most high dose studies have been methodologically defective and would be expected to show a minimum benefit. Clinical studies of divided dose supplementation, predicted on pharmacological grounds to be effective, have only rarely been reported in the literature. Essentially all the claims for high dose vitamin C remain to be scientifically refuted. The clinical effectiveness of large and frequent doses of vitamin C is an open scientific question.

In 2002 a meta-study into all the published research on effectiveness of ascorbic acid in the treatment of infectious disease and toxins was conducted, by Thomas Levy, Medical Director of the Colorado Integrative Medical Centre in Denver. He claimed that evidence exists for its therapeutic role in a wide range of viral infections and for the treatment of snake bites.

Lead poisoning

There is also evidence that Vitamin C is useful in preventing lead poisoning, possibly helping to chelate the toxic heavy metal from the body.

Cancer

In 2005 in vitro research by the National Institutes of Health indicated that Vitamin C administered in pharmacological concentrations (i.e. intravenous) was preferentially toxic to several strains of cancer cells. The authors noted: "These findings give plausibility to intravenous ascorbic acid in cancer treatment, and have unexpected implications for

treatment of infections where H_2O_2 may be beneficial." This research appeared to support Linus Pauling's claims that Vitamin C can be used to fight cancer.[17]

In 2006 the Canadian Medical Association Journal published in vivo research that demonstrated that intravenous vitamin C can subdue advanced-stage cancer. [18]

Cataracts

It has been also suggested that Vitamin C might prevent the formation of cataracts.[19]

Other effects

Contraindications

A Contraindication is a condition which makes an individual more likely to be harmed by a dose of Vitamin C than an average person.

- A primary concern is people with unusual or unaddressed iron overload conditions, including hemochromatosis. Vitamin C enhances iron absorption. If sufferers of iron overload conditions take gram sized doses of Vitamin C, they may worsen the iron overload due to enhanced iron absorption.
- Inadequate Glucose-6-phosphate dehydrogenase enzyme (G6PD) levels, a genetic condition, may predispose some individuals to hemolytic anemia after intake of specific oxidizing substances present in some food and drugs. This includes repeated, very large intravenous or oral dosages of vitamin C. There is a test available for G6PD deficiency. High dose Vitamin E has been proposed as a potential protective factor.

Side-effects

- Vitamin C causes diarrhea in everyone if taken in quantities beyond a certain limit, which is variable to the individual. Cathcart[6] has called this limit the Bowel Tolerance Limit and observed that it is higher in people with serious illness than those in good health. It ranges from 5 to 25 grams per day in healthy individuals to 300 grams per day in the seriously ill persons, such as those with AIDS and cancer. The diarrhea side-effect is harmless, though it can be inconvenient. The diarrhea will cease as soon as the dose is reduced.
- Large doses of vitamin C may cause acid indigestion (stomach upset), particularly when taken on an empty stomach. This unpleasant but harmless side-effect can be avoided by taking the vitamin along with meals, or by offsetting its acidity by taking an antacid such as baking soda or calcium carbonate (Tums)

Effects of Overdose

Vitamin C exhibits remarkably low toxicity. For example, in the rat, the LD50 has been reported as 11900 mg kg-1.[20] For a 70 kg human, this means that 833,000 mg of vitamin C would need to be ingested to stand a 50% chance of killing the person. However, vitamin C could not result in death when administered orally as large amounts of the vitamin cause diarrhea and are not absorbed.[21] An extremely large amount of vitamin C would need to be rapidly injected by IV to stand any chance of killing a person. Robert Cathcart, MD, has used intravenous doses of vitamin C of 250 grams and reports that he has had no problems.[22] The Council for Responsible Nutrition has set an Upper Level (UL) of 2 grams, based on transient diarrhea. Their publication on vitamin C safety notes that "very large doses of vitamin C have been taken daily over the course of many years, and only minor undesirable effects have been attributed with any certainty to the vitamin’s use[...] Clearly, vitamin C has a low order of toxicity".[23]

Alleged harmful effects

Reports of harmful effects of vitamin C tend to receive great prominence in the world's media. As such, these reports tend to generate much debate and more research into Vitamin C. Some of the harmful effects described below have been proven to be unfounded in later studies, while other effects are still undergoing further analysis.

- In April 1998 the journal Nature reported alleged carcinogenic and teratogenic effects of excessive doses of Vitamin C / ascorbic-acid. The effects were noted in test tube experiments and on only two of the 20 markers of free radical damage to DNA. They have not been supported by further evidence from living organisms.[24]
- The authors of the study featured in Nature later clarified their position in correspondence to the journal, stating that their results "show a definite increase in 8-oxoadenine after supplementation with Vitamin C. This lesion is at

least ten times less mutagenic than 8-oxoguanine, and hence our study shows an overall profound protective effect of this vitamin".[25]

- In April 2000, University of Southern California researchers reported a thickening of the arteries of the neck in persons taking high vitamin C doses. It was later pointed out by vitamin C advocates that this can be explained by vitamin C's collagen synthesising role leading to thicker and stronger artery walls. (ref.[26] para 10)
- In June 2004, Duke University researchers reported an increased susceptibility to osteo-arthritis in guinea pigs fed a diet high in vitamin C. However, a 2003 study at Umeå University in Sweden, found that "the plasma levels of vitamin C, retinol and uric acid were inversely correlated to variables related to rheumatoid arthritis disease activity."
- A speculated increased risk of kidney stones may be a side effect of taking Vitamin C in larger than normal amounts (>1g). The potential mechanism of action is through the metabolism of Vitamin C (ascorbic acid) to dehydroascorbic acid, which is then metabolized to oxalic acid,[27] a known constituent of kidney stones. However, this oxalate issue is still controversial, with evidence being presented for[28] and against[29] the possibility of this side effect. Vitamin C has long been advocated,[30] and used,[31] by some less conventional physicians to prevent or alleviate some kinds of non-oxalate kidney stone formation.[32][33] after addressing the oxalate issue.[34][35] Vitamin B6 may mitigate the general risk of oxalate stones by decreasing oxalate production.[36] Additionally, thiamine may inhibit oxalate formation. Furthermore, correcting any magnesium deficiency[37] may decrease the risk of kidney stones by decreasing oxalate crystallization. Increasing one's fluid intake also helps to prevent oxalate crystallization in the kidney. There is evidence that certain intestinal flora influence how much oxalate is destroyed and that their absence is a significant causal risk factor in oxalate stone formers.[38] Patients with a predispostion to form oxalate stones or those on hemodialysis [39][40] should avoid excess use of vitamin C.
- "Rebound scurvy" is a theoretical, never observed, condition that could occur when daily intake of Vitamin C is rapidly reduced from a very large amount to a relatively low amount. Advocates suggest this is an exaggeration of the rebound effect which occurs because ascorbate-dependent enzyme reactions continue for 24-48 hours after intake is lowered, and use up vitamin C which is not being replenished. The effect is to lower one's serum vitamin C blood concentration to less than normal for a short amount of time. During this period of time there is a slight risk of cold or flu infection through reduced resistance. Within a couple of days the enzyme reactions shut down and blood serum returns to the normal level of someone not taking large supplements. This is not scurvy, which takes weeks of zero vitamin C consumption to produce symptoms. It is something people who take large vitamin C supplements need to be aware of in order to gradually reduce dosage rather than quit taking Vitamin C suddenly. (ref.[26] para 4) This is a theoretical risk for those taking supplements - e.g. if

they find themselves severely ill, and in a hospital without the supplements, at a time when they need normal or better levels of vitamin C to fight the disease (ref. [6] and search for "The major problem"). At this time, many doctors and hospital staff do not know much about nor administer megadosing of supplements, so that patients may have to rely on friends or relatives to bring them their supplements.

- Some writers[41] have identified a theoretical risk of poor Copper absorption from high doses of Vitamin C, although little experimental evidence supports this. However, ceruloplasmin levels seem specifically lowered by high vitamin C intake. In one study, 600 milligrams of Vitamin C daily did not decrease copper absorption or overall body copper status in young men, but led to lower ceruloplasmin levels similar to those caused by copper deficiency.[42] In another, ceruloplasmin levels were significantly reduced.[43]
- There are stories circulating among some folk remedy proponents that doses of around 12 grams per day of Vitamin C can induce an abortion in women under 4 weeks of pregnancy.[44] This is not supported by scientific research however.[45]
- Recent studies into the use of a combination of Vitamin E ("natural" source isomer moeity, d-alpha tocopheryl ester) and vitamin C (unspecified ascorbate) in preventing oxidative stress leading to pre-eclampsia have failed to show significant ($p=0.05$) positive benefit at the dosage tested,[46] Drs. Padayatty and Levine with NIH in a "Letter to the Editor" stated that the studies and another "Letter to the Editor" overlooked a key reason for the lack of vitamin C on the prevention of preeclampsia. Because plasma ascorbate concentrations were not reported, we estimated them from known data, the placebo and treatment groups in the study probably had similar plasma and tissue ascorbate concentrations. Doses of 1 g per day have little effect on plasma or intracellular ascorbate concentrations.[47] In another study the same dosage did decrease average gestational time resulting in a higher incidence of low birthweight babies in one study.[48] Several other studies have been more favorable but large studies into antioxidants for pre-eclampsia are continuing.[49]

Conflicts with prescription drugs

Pharmaceuticals designed to reduce stomach acid such as the proton pump inhibitors , e.g. Omeprazole, among the most widely-selling drugs in the world, have been found to lower the bio availability of vitamin C by two thirds. [50]

Sources of vitamin C

Vitamin C is obtained through the diet by the vast majority of the world's population. The richest natural sources are fruits and vegetables, and of those, the camu camu fruit and the billygoat plum contain the highest concentration of the vitamin. It is also present in some cuts of meat, especially liver. Vitamin C is the most widely taken nutritional supplement and

is available in a variety of forms from tablets and drink mixes to pure ascorbic acid crystals in capsules or as plain powder.

Plant sources

Citrus fruits (orange, lemon, grapefruit, lime), tomatoes, and potatoes are good common sources of vitamin C. Other foods that are good sources of vitamin C include papaya, broccoli, brussels sprouts, black currants, strawberries, cauliflower, spinach, cantaloupe, kiwifruit, cranberries and red peppers.

Emblica officinalis often referred to as Indian gooseberry or amla, is one of the richest known sources of vitamin C (720 mg/100g of fresh pulp or up to 900 mg/100g of pressed juice.)– it contains 30 times the amount found in oranges.

The amount of vitamin C in foods of plant origin depends on:

- the precise variety of the plant,
- the soil condition
- the climate in which it grew,
- the length of time since it was picked,
- the storage conditions,
- the method of preparation. Cooking in particular is often said to destroy vitamin C - but see the section on Food preparation.

Animal sources

The overwhelming majority of species of animals and plants synthesise their own vitamin C. It is therefore not a vitamin for them. Synthesis is achieved through a sequence of 4 enzyme driven steps, which convert glucose to ascorbic acid. It is carried out either in the kidneys, in reptiles and birds, or the liver, in mammals and perching birds. The last enzyme in the process, l-gulonolactone oxidase, cannot be made by humans because the gene for this enzyme is defective (Pseudogene ¨GULO). The loss of an enzyme concerned with ascorbic acid synthesis has occurred quite frequently in evolution and has affected most fish; many birds; some bats; guinea pigs; and most primates, including humans. The mutations have not been lethal because ascorbic acid is so prevalent in the surrounding food sources (it may be noted that many of these species' diet consists largely of fruit).

For example an adult goat will manufacture more than 13,000 mg of vitamin C per day in normal health and as much as 100,000 mg daily when faced with life-threatening disease, trauma or stress.

Trauma or injury has been demonstrated to use up large quantities of vitamin C in animals, including humans.

It was only realised in the 1920s that some cuts of meat and fish are also a source of vitamin C for humans. The muscle and fat which make up the modern western diet are however poor sources. As with fruit and vegetables cooking degrades the vitamin C content.

Vitamin C is present in mother's milk and in less amounts in raw cow's milk (but pasteurized milk contains only trace amounts of the vitamin)

The following table shows the relative abundance of vitamin C in various foods of animal origin, given in mg of vitamin C per 100 grams of food:

Food	Amount
Calf liver (raw)	36
Beef liver (raw)	31
Oysters (raw)	30
Cod roe (fried)	26
Pork liver (raw)	23
Lamb brain (boiled)	17
Chicken liver (fried)	13
Lamb liver (fried)	12
Lamb heart (roast)	11

Food	Amount
Lamb tongue (stewed)	6
Human milk (fresh)	4
Goat milk (fresh)	2
Cow milk (fresh)	2
Beef steak (fried)	0
Hen's egg (raw)	0
Pork bacon (fried)	0
Calf veal cutlet (fried)	0
Chicken leg (roast)	0

Food preparation

It is important to choose a suitable method of food preparation that conserves vitamin C content. When cooking vegetables, one should seek to minimize temperature and duration of cooking and not discard water used in preparation (e.g., by steam cooking or by making soup). Food source vitamin C is identical to that in supplements. The structure of vitamin C is well understood, see ascorbic acid, and there is no difference in benefit between natural and synthetic forms (although fruits and vegetables contain various other nutrients, and vitamin C is not their only health benefit).

Recent observations suggest that the impact of temperature and cooking on vitamin C may have been overestimated:

1. Since it is water soluble, vitamin C will strongly leach into the cooking water while cooking most vegetables — but this doesn't necessarily mean the vitamin is destroyed — it's still there, but it's in the cooking water. (This may also suggest how the apparent misconception about the extent to which boiling temperatures destroy vitamin C might have been the result of flawed research: If the vitamin C content of vegetables (and not of the water) was measured subsequent to cooking them, then that content would have been much lower, though the vitamin has not actually been destroyed .)
2. Not only the temperature, but also the exposure time is significant. Contrary to what was previously and is still commonly assumed, it can take much longer than two or three minutes to destroy vitamin C at boiling point

It also appears that cooking doesn't necessarily leach vitamin C in all vegetables at the same rate; it has been suggested that the vitamin is not destroyed when boiling broccoli.[51] This may be a result of vitamin C leaching into the cooking water at a slower rate from this vegetable.

Copper pots will destroy the vitamin.[52]

Some research shows that fresh-cut fruit may not lose much of its nutrients when stored in the refrigerator for a few days.[53]

Vitamin C enriched teas and infusions have increasingly appeared on supermarket shelves. Such products would be nonsense if boiling temperatures did indeed destroy vitamin C at the rate it had previously been suggested. It should be noted however that as of 2004 most academics not directly involved in vitamin C research still teach that boiling temperatures will destroy vitamin C very rapidly.

Vitamin C supplements

Vitamin C is the most widely taken dietary supplement.[54] It is available in many forms including caplets,tablets, capsules, drink mix packets, in multi-vitamin formulations and as chemically pure crystaline powder. Tablet and capsule sizes range from 25mg to 1500mg. Vitamin C (ascorbic acid) crystals are typically available in bottles containing 300g to 1 kg of powder (a teaspoon of vitamin C crystals equals 4,500mg).

Methods of manufacture (chemical synthesis)

Vitamin C is produced from glucose by two main routes. The Reichstein process developed in the 1930s uses a single pre-fermentation followed by a purely chemical route. The more modern Two-Step fermentation process was originally developed in China in the 1960s, uses additional fermentation to replace part of the later chemical stages. Both processes yield approximately 60% vitamin C from the glucose feed.[55]

Research is underway at the Scottish Crop Research Institute to create yeast micro organisms to synthesise ascorbic acid in a single fermentation step, a technology which is expected to reduce manufacturing costs considerably.[56]

World production of synthesised vitamin C is currently estimated at approximately 110,000 tonnes annually. Main producers today are BASF/Takeda, DSM, Merck and the China Pharmaceutical Group Ltd. of the People's Republic of China. China is slowly becoming the major world supplier as its prices undercut those of the US and European manufacturers.[57]

Discovery and history

The need to include fresh plant food or raw animal flesh in the diet to prevent disease was known from ancient times. Native peoples living in marginal areas incorporated this into their medicinal lore. For example, infusions of spruce needles were used in the temperate zones, or the leaves from species of drought-resistant trees in desert areas. In 1536, the French explorer Jacques Cartier, exploring the St. Lawrence River, used the local natives' knowledge to save his men who were dying of scurvy. He boiled the needles of the arbor vitae tree to make a tea that was later shown to contain 50 mg of vitamin C per 100 grams.[58][59]

Through history the benefit of plant food for the survival of sieges and long sea voyages was recommended by enlightened authorities. John Woodall, the first appointed surgeon to the British East India Company, recommended the use of lemon juice as a preventive and cure in his book "The Surgeon's Mate" of 1617. The Dutch writer, Johann Bachstrom of Leyden, in 1734, gave the firm opinion that "scurvy is solely owing to a total abstinence from fresh vegetable food, and greens; which is alone the primary cause of the disease."

The first attempt to give scientific basis for the cause of scurvy was by a ship's surgeon in the British Royal Navy, James Lind. While at sea in May 1747, Lind provided some crew members with two oranges and one lemon per day, in addition to normal rations, while others continued on cider, vinegar or sea water, along with their normal rations. In the history of science this is considered to be the first example of a controlled experiment comparing results on two populations of a factor applied to one group only with all other factors the same. The results conclusively showed that citrus fruits prevented the disease. Lind wrote up his work and published it in 1753, in Treatise on the Scurvy.

Lind's work was slow to be noticed, partly because he gave conflicting evidence within the book and partly because of social inertia in some elements at the British admiralty who saw care for the well-being of ships' crew as a sign of weakness. There was also the fact that fresh fruit was very expensive to keep on board, whereas boiling it down to juice allowed easy storage but destroyed the vitamin. Ships' captains assumed wrongly that it didn't work, because the juice failed to cure scurvy.

It was 1795 before the British navy adopted lemons or lime as standard issue at sea. Limes were more popular as they could be found in British West Indian Colonies, unlike lemons which weren't found in British Dominions, and were therefore more expensive. (This practice led to the nickname limey for British people, especially British sailors.) Captain James Cook had previously demonstrated and proven the principle of the advantages of fresh and preserved foods, such as sauerkraut, by taking his crews to the Hawaiian islands and beyond without losing any of his men to scurvy. For this otherwise unheard of feat, he was awarded a medal by the British Admiralty. So the Navy was certainly well aware of the principle. The cost of providing fresh fruit on board was probably a factor in this long delay. Luxuries or non-standard supplies not provided by the Admiralty were usually provided by the Captains.

The name "antiscorbutic" was used in the eighteenth and nineteenth centuries as general term for those foods known to prevent scurvy, even though there was no understanding of the reason for this. These foods include lemons, limes, and oranges; sauerkraut, salted cabbage, malt, and portable soup were employed with variable effect.

In 1907, Axel Holst and Theodor Frølich, two Norwegian biochemists studying beriberi contracted aboard ship's crews in the Norwegian Fishing Fleet, wanted a small test mammal to substitute for the pigeons they used. They fed guinea pigs the test diet, which had earlier produced beriberi in their pigeons, and were surprised when scurvy resulted instead. Until that time scurvy had not been observed in any organism apart from humans, and it was considered an exclusively human disease.

In the early twentieth century, the Polish-American scientist Casimir Funk conducted research into deficiency diseases, and in 1912 Funk developed the concept of vitamins, for the elements in food which are essential to health. Then, from 1928 to 1933, the Hungarian

research team of Joseph L Svirbely and Albert Szent-Györgyi and, independently, the American Charles Glen King, first isolated vitamin C and showed it to be ascorbic acid.

In 1928 the arctic anthropologist and adventurer Vilhjalmur Stefansson attempted to prove his theory of how Eskimo (Inuit) people are able to avoid scurvy with almost no plant food in their diet. This had long been a puzzle because the disease had struck European Arctic explorers living on similar high-meat diets. Stefansson theorised that the native peoples of the Arctic got their vitamin C from fresh meat that was raw or minimally cooked. Starting in February 1928, for one year he and a colleague lived on an animal-flesh-only diet under medical supervision at New York's Bellevue Hospital; they remained healthy.

In 1933-1934, the British chemists Sir Walter Norman Haworth and Sir Edmund Hirst and, independently, the Polish Tadeus Reichstein, succeeded in synthesizing the vitamin, the first to be artificially produced. This made possible the cheap mass production of vitamin C. Haworth was awarded the 1937 Nobel Prize in Chemistry largely for this work. The synthetic form of the vitamin is identical to the natural form.

The Swiss pharmaceutical company Hoffmann-La Roche was the first to mass produce synthetic vitamin C, under the brand name of Redoxon, in 1934.

In 1959 the American J.J. Burns showed that the reason some mammals were susceptible to scurvy was the inability of their liver to produce the active enzyme L-gulonolactone oxidase, which is the last of the chain of four enzymes which synthesize ascorbic acid.

American biochemist Irwin Stone was the first to exploit Vitamin C for its food preservative properties and held patents on this. He developed the theory that vitamin C was an essential nutrient deficient in humans as a result of a genetic defect that afflicted the whole human race.

Vitamin C hypothesis

Since its discovery Vitamin C has been considered a universal panacea by some, although this led to suspicions of it being overhyped by others.[60]

The fact that man possesses three of the four enzymes that animals employ to manufacture ascorbates in relatively large amounts, has led researchers such as Irwin Stone and Linus Pauling to hypothesize that man's ancestors once manufactured this substance in the body millions of years ago in quantities roughly estimated at 3,000-4,000 mg daily, but later lost the ability to do this through a chance of evolution. If true, this would mean that vitamin C was misnamed as a vitamin and is in fact a vital macronutrient like fat or carbohydrate.{Irwin Stone: "The Healing Factor"}

Dr. Hickey, of Manchester Metropolitan University, believes that man carries a mutated and ineffective form of the genetic machinery for manufacturing the fourth of the four enzymes used by all mammals to make ascorbic acid. Cosmic rays or a retro virus could have caused this mutation, millions of years ago.{Hickey: "Ascorbate"} In humans the three surviving enzymes continue to produce the precursors to ascorbic acid but the process is incomplete and the body then disassembles them.

In the 1960s Nobel-Prize winning chemist Linus Pauling, after contact with Irwin Stone, began actively promoting vitamin C as a means to greatly improve human health and resistance to disease. His book How to Live Longer and Feel Better was a bestseller and advocated taking more than 10,000 milligrams per day. It sold widely and many advocates

today see its influence as the reason there was a marked downward trend in US heart disease from the early 1980s onwards.

Stone's work also informed the practise of Dr. Robert F. Cathcart III, in the 1970s and 1980s. He applied extremely large doses of ascorbate (300 grams = 0.66 pounds per day) to a wide range of viral diseases with successful results. Cathcart developed the concept of Bowel tolerance, the use of the onset of diarrhea as an indication of when the body's true requirement of ascorbic acid had been reached. He found that seriously ill people could often tolerate levels of tens of grams per day before their tolerance limit is reached.

Matthias Rath is a controversial German physician who once worked with Pauling. He is an active proponent and publicist for high dose vitamin C. He has published a theory that deaths from scurvy in humans during the ice age, when vitamin C was scarce, selected for individuals who could repair arteries with a layer of cholesterol. He theorises that, although eventually harmful, cholesterol lining of artery walls would be beneficial in that it would keep the individual alive until access to Vitamin C allowed arterial damage to be repaired. Atherosclerosis is thus a vitamin C deficiency disease. Rath has also argued publicly that high doses of vitamin C can be effectively used against viral epidemics such as HIV,[61] SARS and bird flu.[62][63]

It has been suggested by some advocates that ascorbic acid is really a food group in its own right like carbohydrates or protein and should not be seen as a pharmaceutical or vitamin at all.{Irwin Stone: "The Healing Factor"}

Chronic scurvy

Identified and named by Linus Pauling, "chronic scurvy" or "subclinical scurvy" is a condition of Vitamin C deficiency which is not as easily noticeable as acute scurvy (because chronic scurvy is mostly internal), characterized by micro lesions of tissues (such as that caused by blood pulsing through arteries, which stretches the arterial walls causing them to tear slightly). It is a major contributing factor to cardio vascular disease. The condition is almost entirely preventable with supplementation of larger doses of Vitamin C (8 grams or more per day). Chronic scurvy is commonplace, even in industrialized countries.

Politics of Vitamin C

Regulation

There are regulations in most countries which limit the claims on the treatment of disease that can be placed on food, drug, and nutrient product labels. Regulations include:

- Claims of therapeutic effect with respect to the treatment of any medical condition or disease are prohibited by the Food and Drug Administration (in the USA, and by the corresponding regulatory agencies in other countries) unless the substance has gone through a lengthy (10+ years) and expensive (200 million US dollars+) approval process, for which the applicant seeking approval must pay.

- In the United States, the following notice is mandatory on food, drug, and nutrient product labels which make health claims: These statements have not been evaluated by the Food and Drug Administration. This product is not intended to diagnose, treat, cure or prevent any disease. This statement must be included even if substantial scientific evidence exists showing that the message isn't true. This may lead consumers to the false belief that Vitamin C has no value in preventing or treating diseases other than scurvy (for which treatment claims are allowed).

Advocacy arguments

Vitamin C advocates argue that there is a large body of scientific evidence that the vitamin has a wide range of health and therapeutic benefits but which they claim have been ignored. They claim the following factors affect the marketing and distribution of Vitamin C, and the dissemination of information concerning the nutrient:

- There is increasing evidence of the applications and efficacy of Vitamin C, but governmental agency dose and frequency of intake recommendations have remained relatively fixed. This has lead some researchers to challenge the recommendations. In 2003 Steve Hickey and Hilary Roberts of the Manchester Metropolitan University published a fundamental criticism of the approach taken to fix the nutritional requirement of vitamin C. They again argued in 2004 that the RDA which is based on blood plasma and white blood cell saturation data from the National Institutes of Health (NIH) was based on flawed data.[64] According to these authors, the doses required to achieve blood, tissue and body "saturation" are much larger than previously believed. They allege that the Institute of Medicine (IoM) and the NIH have failed to respond to an open letter from a number of scientists and medical researchers, notably Doctors Steve Hickey, Hilary Roberts, Ian Brighthope, Robert Cathcart, Abram Hoffer, Archie Kalokerinos, Tom Levy, Richard Passwater, Hugh Riordan, Andrew Saul and Patrick Holford, which called for revision of the RDI (Reference Daily Intake).
- Research and the treatment approval process are so expensive, pharmaceutical companies rarely apply for approval of an unpatentable product. To do so without the protection of a patent would allow competitors to manufacture the product too, which would drive the price (and profit margin) down to a point much less desirable than the price point (and profit margin) of patentable products. The lower price would also reduce the likelihood of recuperating the company's exorbitant research funding and treatment approval costs. Vitamin C is not eligible for patenting because it is a natural substance, and because it has already been marketed to the public for some time. As of yet, no company has applied to the FDA (nor paid) for approval of Vitamin C as a treatment for any disease.
- Companies selling a treatment product are not required to inform consumers or patients of other treatments, even if those treatments are more effective, less expensive, and have fewer side-effects. Medical practitioners are

not required to inform their patients of treatments for which treatment approval has not been granted. This situation, coupled with the label censorship explained above makes it more difficult to keep the public informed about the benefits of and new discoveries concerning the applications and effective dosage levels of Vitamin C.

- Matthias Rath and others point to low doses of Vitamin C as the cause of the current epidemics of heart disease and cancer, and have termed the situation "a genocide", implying that health care providers (and particularly cardiologists and pharmaceutical companies) are aware of Vitamin C's benefits and are deliberately seeking to block its acceptance as a therapeutic agent.[65] Meanwhile, governments, with their bureaucratic systems of treatment approval filtering out natural and inexpensive treatments such as those applying vitamin C, have also contributed to this technology blockade.

See also

- Vitamin

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